Procalcitonin as a marker of diabetic foot ulcer infection

Nabil A. El-Kafrawy[a], Mohammed A. Shaaban[a], Mohammed A. Korany[a], Ahmed A. Sonbol[b], Moustafa B. Ata[a]

Departments of [a]Internal Medicine, [b]Clinical Pathology, Faculty of Medicine, Menoufia University, Shebeen El-Kom, Egypt

Correspondence to Moustafa B. Ata, MSc, Shebeen El-Kom, Menoufia, 32511, Egypt. Tel: +20 100 696 5686; e-mail: dr_house210@yahoo.com

Received 16 February 2019
Accepted 20 February 2019
Published: 18 August 2020

The Egyptian Journal of Internal Medicine
2019, 31:652–657

Background
Procalcitonin (PCT), an amino acid protein precursor of calcitonin hormone released by thyroid C cells or other body cells, can be used as a marker for diagnosing infection. PCT has a suggestive role in diagnosing diabetic foot infection alone or in combination with other markers of infection.
Objective
The aim was to clarify the effectiveness of PCT as a marker for diagnosing of infection in Egyptian patients with diabetic foot ulcer (DFU) in comparison with other inflammatory markers such as C-reactive protein, white blood cell count, and erythrocyte sedimentation rate.
Patients and methods
This cross-sectional study was carried out at Menoufia University Hospitals, from the period of January 2018 to December 2018. In total, 90 patients were classified into three groups; each group contained 30 patients: group I served as diabetic control without foot ulcers, group II patients had noninfected DFU, and group III patients had infected diabetic foot ulcer (IDFU). Diagnosis of IDFU relied on Infectious Diseases Society of America-International Working Group on the Diabetic Foot classification of diabetic foot infection.
Results
Serum PCT levels were elevated in DFU groups, with significantly higher in infected more than noninfected DFU. In addition, PCT levels were significantly higher in patients with IDFU compared with traditional markers such as C-reactive protein, erythrocyte sedimentation rate, and white blood cell counts.
Conclusion
Based on our results, we conclude that PCT has a valuable role in diagnosing infection in DFUs.

Keywords:
diabetic foot ulcer infection, inflammatory markers, procalcitonin

Egypt J Intern Med 31:652–657

1110-7782

Introduction

Diabetic foot infection is an increasing problem. With progression of infection, which may lead to hospitalization of the patients, surgical intervention and amputation become necessary [1]. Unfortunately, the life quality of lower limb-amputated patients is quite poor [2]. Therefore, diabetic foot wound needs careful assessment for presence of infection and classification of the severity of the infection when present. There are multiple classifications, such as Infectious Diseases Society of America-International Working Group on the Diabetic Foot (IDSA-IWGDF), which is a clinical classification system of diabetic foot according to the infection severity [3]. These classification schemes are effective and helpful for their prognosis and assessment of need of amputation in patients with diabetic foot [4]. Diagnosis of IDFU depends on clinical findings and microbiological findings [5]. Infection can markedly break down patient's condition, so it is important to diagnose IDFU early [6]. Procalcitonin (PCT) is the precursor of calcitonin hormone synthesized by para-follicular C-cells in the thyroid gland [7]. PCT production by blood mononuclear cells increases after inflammation occurs and is modulated by lipopolysaccharides and cytokines during sepsis [8]. PCT may have a role in the early diagnosis of IDFU [9,10]. PCT is an accurate marker for diagnosing infections compared with C-reactive protein (CRP) [11]. Nevertheless, in another study, it was reported that PCT has limited role in the discrimination of degree of severity of diabetic foot infection [12]. As there are conflicting results and limited studies concerning the use of PCT in the diagnosis of IDFU, more specific studies are needed on this patient population. We aimed to clarify the usefulness of PCT as a marker for diagnosing the

presence of infection in Egyptian patients with DFU in comparison with other traditional inflammatory markers such as CRP, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count.

Patients and methods

This is a cross-sectional study carried out at Menoufia University Hospitals from January 2018 to December 2018. 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. This study included 90 patients, divided into three groups: group I included 30 diabetic control patients who had no DFU, group II included 30 patients with noninfected diabetic foot ulcers (NIDFU), and group III included 30 patients with IDFU. IDFU diagnosis was based on IDSA-IWGDF classification of foot infections.

Patients with the following criteria were excluded: current inflammatory bowel disease, pneumonia, meningitis, gestational diabetes, and who underwent surgery in the past 2–3 weeks.

All patients underwent full history taking and clinical examination including measurement of blood pressure, weight, and height. BMI was calculated as weight (kg)/height (m^2). Diabetic complications (retinopathy, nephropathy, and cardiovascular diseases) were documented for all groups.

Regarding laboratory assessment, blood samples were taken from all patients for measurements of complete blood count, inflammatory markers (PCT, ESR, and CRP), fasting blood glucose, 2-h postprandial blood glucose, glycated hemoglobin (HbA1c), kidney functions (urea and creatinine), and lipid profile (total cholesterol, triglycerides, and low-density lipoprotein cholesterol) before the eventual initiation of antimicrobial treatment. Laboratory investigation included the following: ESR, CRP, fasting blood glucose, 2-h postprandial blood glucose, HbA1c, lipid profile, and kidney function were carried out by Dimension RxL Max analyzer (Siemens Health GmbH-Henkestr, Erlangen, Germany) by colorimetric techniques. HbA1c percentages were determined by using cation exchange resin. For analyzing the PCT levels, blood samples were collected and centrifuged for 20 min at 4000 rpm. The serum PCT levels were tested using using enzyme-linked immunosorbent assay technique kit (Chongqing Biospes, Chongqing, China), with a sensitivity limit of 0.02 ng/ml.

Statistical analysis

Data entry, coding, and analysis were assessed using SPSS for Windows (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. *P* value up to 0.05 was considered significant and value up to 0.001 was considered highly significant.

Table 1 Demographic and clinical data of the studied groups (*N*=90)

Variables	Groups			Test of significance	*P* value
	Group I (*N*=30)	Group II (*N*=30)	Group III (*N*=30)		
Age (mean±SD) (years)	46.9±5.11	47.8±6.65	49.3±7.83	0.97[a]	0.380
Sex [*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)		
SBP (mean±SD) (mmHg)	126.4±17.5	127.3±12.8	130.1±11.3	0.784[a]	0.460
DBP (mean±SD) (mmHg)	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
Diabetic complication and comorbidities [*n* (%)]					
Nephropathy	10 (33.3)	12 (40.0)	15 (50.0)	3.45[b]	0.968
Retinopathy	6 (20.0)	4 (13.3)	5 (16.7)		
Nephropathy and retinopathy	4 (13.3)	3 (10.0)	3 (10.0)		
Myocardial ischemia	5 (16.7)	4 (13.3)	4 (13.3)		
CAD	3(10.0)	4 (13.3)	2 (6.70)		
CVD	2 (6.70)	3 (10.0)	1 (3.30)		

CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure. $P>0.05$, NS.
[a]Analysis of variance test. [b]χ^2-Test.

Results

There were no significant statistically differences between studied groups regarding demographic data (age and sex), clinical data (BMI and blood pressure), and comorbidities (nephropathy, retinopathy, and cardiovascular diseases) (Table 1).

Regarding laboratory investigations among the studied groups, there was a significant difference regarding hemoglobin and platelets, serum creatinine, fasting blood glucose, and 2-h postprandial blood glucose ($P \leq 0.05$; Table 2).

The comparative profile of circulating levels of inflammatory markers in the study groups showed there was a significant difference regarding ESR levels and WBC count ($P \leq 0.05$) and highly significant difference regarding PCT levels and CRP concentration ($P \leq 0.001$; Table 3).

Binary logistic regression analysis was done to detect predictable factors for infection among DFU patients, and we found that PCT and CRP were the most predictable factors for infection among patients with diabetic ulcer (Table 4).

Table 2 Laboratory investigations among the studied groups (*N*=90)

Variables	Groups			Test of significance	*P* value	Post-hoc test
	Group I (*N*=30)	Group II (*N*=30)	Group III (*N*=30)			
Fasting blood glucose (mean±SD) (mg/dl)	137.9±24.7	151.8±36.0	155.9±24.4	3.19[a]	0.046	P_1: 0.066P_2: 0.018*P_3: 0.581
2-h postprandial blood glucose (mean±SD) (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 (mean±SD) (%)	8.11±0.60	8.45±0.72	8.53±0.95	1.62[a]	0.204	P_1: 0.089P_2: 0.190P_3: 0.689
Total cholesterol (mean±SD) (mg/dl)	236.6±19.1	233.4±20.1	243.4±20.9	1.95[a]	0.148	P_1: 0.558P_2: 0.193P_3: 0.056
Triglycerides (mean±SD) (mg/dl)	208.9±33.4	209.9±34.3	227.1±32.8	3.89[a]	0.067	P_1: 0.907P_2: 0.015*P_3: 0.051
LDL-C (mean±SD) (mg/dl)	121.6±22.4	129.2±24.2	131.1±25.2	1.30[a]	0.278	P_1: 0.224P_2: 0.132P_3: 0.768
Urea (mean±SD) (mg/dl)	32.0±5.21	33.3±5.48	34.7±5.88	1.74[a]	0.181	P_1: 0.353P_2: 0.065P_3: 0.352
Creatinine (mean±SD) (mg/dl)	1.21±0.25	1.23±0.29	1.40±0.35	3.48[a]	0.035	P_1: 0.832P_2: 0.019*P_3: 0.043*
Hemoglobin (mean±SD) (g/dl)	11.2±1.32	10.6±1.01	10.3±1.46	3.40[a]	0.038	P_1: 0.077P_2: 0.012*P_3: 0.254
Platelet (mean±SD) ($\times 10^9$/l)	277.7±68.2	297.3±64.1	325.7±83.0	3.34[a]	0.040	P_1: 0.297P_2: 0.012*P_3: 0.132

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.

Table 3 Inflammatory markers among the studied groups (*N*=90)

Variables	Groups			Test of significance	*P* value	Post-hoc test
	Group I (*N*=30)	Group II (*N*=30)	Group III (*N*=30)			
WBC (mean±SD) ($\times 10^9$/l)	8.22±2.19	8.66±2.57	10.2±3.18	4.48[a]	0.014	P_1: 0.530P_2: 0.005*P_3: 0.029*
ESR (mean±SD) (mm/h)	40.9±10.1	43.0±12.1	49.0±9.24	3.51[a]	0.034	P_1: 0.438P_2: 0.011*P_3: 0.035*
CRP (mean±SD) (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 (mean±SD) (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**

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IDFU, infected diabetic foot ulcer; NIDFU, noninfected diabetic foot ulcers; PCT, procalcitonin; WBC, white blood cell. [a]Analysis of variance test. [b]Kruskal–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. *$P \leq 0.05$, significant. **$P \leq 0.001$, highly significant.

The receiver operating characteristic (ROC) curve analysis of inflammatory marker for detection of infection was done among DFUs. PCT had higher area under curve (AUC), sensitivity, specificity, and accuracy more than CRP concentration, WBC count, and ESR levels, correspondingly (Table 5 and Fig. 1).

Discussion

Diabetic foot infection and ulcers are common complication of diabetes mellitus with a difficult prolonged healing process and chronic pattern [13]. 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 as bone may be involved [14]. Diagnosis of IDFU is usually clinically based but somewhat may be confusing [15]. PCT is produced in direct response to bacterial endotoxins and indirectly to mediators such as interleukin (IL)-1β, tumor necrosis factor-α, and IL-6, and it is strongly correlated with severity of infection [16]. The aim of the study was to clarify the effectiveness of PCT as an inflammatory marker in diagnosing infection among Egyptian IDFU patients in comparison with traditional inflammatory markers such as CRP, WBC, and ESR.

A group of control diabetic patients without foot complication were enrolled to exclude the inflammatory state accompanying diabetes mellitus that may cause an increase of PCT concentration. Considering PCT level, in group I, it ranged from 0.02 to 0.30, whereas in group II, PCT concentration ranged from 0.04 to 0.90 ng/ml, and in group III, it ranged from 0.35 to 2.26 ng/ml, with a highly statistically significant difference ($P \leq 0.001$). This finding is in agreement with Uzun *et al.* [11] and Massara *et al.* [15] who detected that PCT had higher efficiency in distinguishing IDFU from NIDFU. In addition, Massara *et al.* [15] reported increased sensitivity when PCT is combined with CRP or ESR.

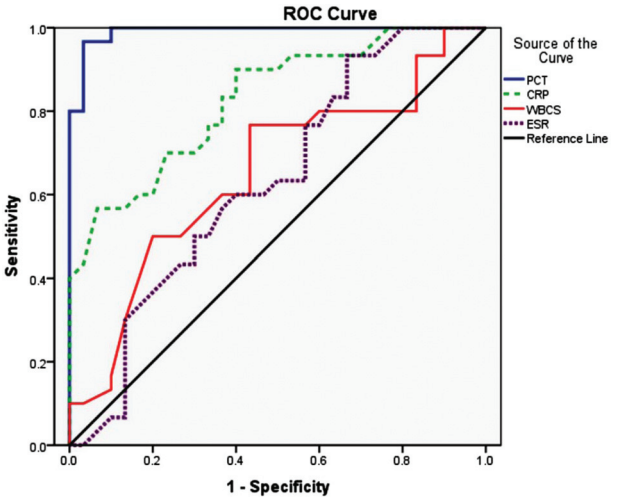
Regarding CRP concentration, it had a higher statistically significant difference in group III than the other groups. This is in agreement with Park *et al.* [17] who found PCT and CRP measurement correlated positively with the grades of infection of DFUs. CRP was useful for distinguishing localized diabetic foot infection grades.

Table 4 Multivariate logistic regression analysis to detect predictable factors for infection among patients with diabetic ulcer

Predictors	β	Wald	*P* value	95% CI
WBC (×10^9/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

CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; WBC, white blood cell.
*Significant difference. **Highly significant.

Figure 1



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.

Table 5 Receiver operating characteristic curve analysis of inflammatory marker for detection of infection among patients with diabetic ulcer (*N*=60)

Inflammatory marker	AUC	Cutoff 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
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.

WBC count and ESR levels were also markers of infection as confirmed in our study, in which WBC count and ESR levels were significantly higher in group III in comparison with other groups.

The findings of this study revealed PCT is a valuable diagnostic marker with higher AUC, sensitivity, and specificity in differentiating infected from noninfected DFUs. For PCT, the AUC_{ROC}, 0.946, was found to be greater than for other traditional markers. In addition, PCT had 93% sensitivity, 83% specificity, 85% PPV, 93% NPV, and 88% accuracy at a cutoff point of 0.60 ng/ml to diagnose infection.

This is in agreement with Umapathy *et al.* [18] who found that PCT can be used as a good marker for realizing infection in Indian patients with DFU and it was greater than for other traditional markers. They found PCT AUC_{ROC}, sensitivity, specificity, PPV, NPV and accuracy was 0.99, 54, 100, 100, 12, and 95%, respectively, at a cutoff point of 0.5 ng/ml.

Another study by Jafari *et al.* [10] reported that PCT is a prognostic marker in distinguishing IDFU and NIDFU in combination with CRP concentration and ESR. Surprisingly, ESR was the most sensitive and specific inflammatory marker distinguishing IDFU from NIDFU. They further reported that a threshold PCT value of 0.21 ng/ml exhibited a sensitivity and specificity of 70 and 74%, respectively.

In contrary to our findings and previous studies, Jeandrot *et al.* [12] found that PCT is not a superior marker in comparison with other markers like CRP and WBC count in discrimination between IDFU from NIDFU. They suggested CRP to be a valuable marker in distinguishing IDFU from NIDFU because it had high specificity and sensitivity compared with other markers. The high performance of CRP, compared with PCT, could be explained by the mild nature of infection in grade 2 diabetic foot ulcers: CRP values were shown to increase significant in response to localized infection, whereas local infection lacking systemic manifestations results only in mild increase in PCT levels [19]. In the study by Karakas *et al.* [20], PCT could not predict lower extremity amputation in patients admitted with diabetic foot ulcers. This can be explained by small size of sample, because only six of the 27 patients being in the study required amputation. IL-6 level had a statistically significant forecaster of amputation existence in these patients.

Our study limitation was that grading of infection severity of DFUs depended on clinical examination guided by only IDSA-IWGDF clinical classification as interobserver variability difference in grading infection severity may occur.

To that end, the usefulness of PCT is still controversial, as it is subjected to changes owing to age, pathogen, and site and type of infection. Therefore, more research studies are needed to evaluate the diagnostic validity of PCT in diagnosing IDFU patients.

Conclusion

Our study concluded that PCT levels had higher efficiency in distinguishing between IDFU from NIDFU followed by CRP, WBC, and ESR levels.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Pemayun TG, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case-control study. Diabet Foot Ankle 2015; 6:29629.

2 Suckow BD, Goodney PP, Nolan BW, Veeraswamy RK, Gallagher P, Cronenwett JL, *et al.* Domains that determine quality of life in vascular amputees. Ann Vasc Surg 2015; 29:722–730.

3 Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, *et al.* Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012; 54: e132–e173.

4 Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes Metab Res Rev 2014; 30:610–622.

5 Abbas M, Uckay I, Lipsky BA. In diabetic foot infections antibiotics are to treat infection, not to heal wounds. Expert Opin Pharmacother 2015; 16:821–832.

6 Singh S, Pai DR, Yuhhui C. Diabetic foot ulcer – diagnosis and management. Clin Res Foot Ankle 2013; 1:120.

7 Saleem SM, Khan SS, Jan SS. Role of serum procalcitonin level in early diagnosis of bacterial pneumonia in children, a hospital-based study. Int J Res Med Sci 2016; 4:1518–1521.

8 Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, *et al.* Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. J Lab Clin Med 1999; 134:49–55.

9 Velissaris D, Pantzaris ND, Platanaki C, Antonopoulou N, Gogos C. Procalcitonin as a diagnostic and prognostic marker in diabetic foot infection. A current literature review. Rom J Intern Med 2018; 56:3–8.

10 Jafari NJ, Firouzabadi MS, Izadi M, Firouzabadi MS, Saburi A. Can procalcitonin be an accurate diagnostic marker for the classification of diabetic foot ulcers?. Int J Endocrinol Metab 2014; 12:e13376.

11 Uzun G, Solmazgul E, Curuksulu H, Turhan V, Ardic N, Top C, *et al.* Procalcitonin as a diagnostic aid in diabetic foot infections. Tohoku J Exp Med 2007; 213:305–312.

12 Jeandrot A, Richard JL, Combescure C, Jourdan N, Finge S, Rodier M, *et al.* Serum procalcitonin and C-reactive protein concentrations to distinguish mildly infected from non-infected diabetic foot ulcers: a pilot study. Diabetologia 2008; 51:347–352.

13 Gary Sibbald R, Woo KY. The biology of chronic foot ulcers in persons with diabetes. Diabetes Metab Res Rev 2008; 24 (S1):S25–S30.

14 Noor S, Zubair M, Ahmad J. Diabetic foot ulcer – a review on pathophysiology, classification and microbial etiology. Diabetes Metab Syndr 2015; 9:192–199.

15 Massara M, De Caridi G, Serra R, Barillà D, Cutrupi A, Volpe A, *et al.* The role of procalcitonin as a marker of diabetic foot ulcer infection. Int Wound J 2017; 14:31–34.

16 Christ-Crain M, Muller BE. Procalcitonin in bacterial infections-hype, hope, more or less?. Swiss Med Wkly 2005; 135:451–460.

17 Park JH, Suh DH, Kim HJ, Lee YI, Kwak IH, Choi GW. Role of procalcitonin in infected diabetic foot ulcer. Diabetes Res Clin Pract 2017; 128:51–57.

18 Umapathy D, Dornadula S, Rajagopalan A, Murthy N, Mariappanadar V, Kesavan R, *et al.* Potential of circulatory procalcitonin as a biomarker reflecting inflammation among South Indian diabetic foot ulcers. J Vasc Surg 2018; 67:1283–1291.

19 Rothenburger M, Markewitz A, Lenz T, Kaulbach HG, Marohl K, Kuhlmann WD, *et al.* Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein. Clin Chem Lab Med 1999; 37:275–279.

20 Karakas A, Arslan E, Cakmak T, Aydin I, Akgul EO, Demirbas S. Predictive value of soluble CD14, interleukin-6 and procalcitonin for lower extremity amputation in people with diabetes with foot ulcers: a pilot study. Pak J Med Sci 2014; 30:578–582.