Serum Procalcitonine level in diabetic foot patients

Sama Fathy Mohamed *[1], Nashwa Mohamed Aboalnasr[1], Loai Mohamed El-Ahwal[1], Mamdouh Radwan El-Nahas[2], Saharmohey El-Din Hazzaa[3]

[1]Department of internal medicine, Tanta University, Faculty of Medicine, Egypt.
[2] Department of internal medicine, Port said University, Faculty of Medicine, Egypt.
[3]Department of Clinical Pathology, Tanta University, Faculty of Medicine, Egypt.
dr.samamostafa@gmail.com

Abstract: Background: Diabetes represents an emerging global epidemic and one of the leading causes of morbidity and mortality. Although many serious complications, such as kidney failure or blindness, can affect individuals with diabetes, it is the complications of foot that take the greatest toll. Currently it can be estimated that millions of people are or will be affected by diabetic foot. Up to 66% of the persons admitted to the hospital with a diabetic foot infection have osteomyelitis. Its presence increases morbidity, risk of amputation and mortality. Charcot neuro-osteoarthropathy is another devastating complication of diabetic peripheral neuropathy which can be another important cause of amputation. In spite differentiation between CN and OM is often obvious, but it still difficult in many cases. **Aim of the work:** we aimed to assess the value of Procalcitonine (PCT) to distinguish acute osteomyelitis from acute Charcot arthropathy. **Patients and methods:** Our study included 90 patients, acute Charcot group (30 patients) and acute osteomyelitis group (30 patients). 30 diabetic patients, all were recruited from Tanta and Mansoura university Hospital (diabetic foot clinic, diabetes outpatient clinics and inpatient wards); All patients were subjected to thorough full history taking, complete clinical examination, and laboratory investigation including FBG, HbA1c, CBC, serum creatinine, liver function tests, ESR and CRP as well as serum levels of Procalcitonine. We studied the role of the inflammatory markers (ESR, CRP, TLC and PCT) in the differentiation between the Charcot group and osteomyelitis group. **Result:** We found that TLC showed non-significant difference between study groups (P = 0.144) as it was of limited sensitivity for the diagnosis of osteomyelitis. ESR levels were significantly higher in the OM group in comparison to the Charcot and control group *(P= 0.000)* and the cut-off value of ESR to diagnose OM was 22.50 mm/hr. CRP levels were significantly higher in the OM group in comparison to the Charcot and control group *(P= 0.000)*, Cut-off value of CRP to diagnose acute OM was 19.5 mg/l.PCT levels were significantly higher in the OM group in comparison to the Charcot and control group *(P= 0.000)*, and the best cut-off value of PCT to diagnose a case of acute OM was 0.2 ng/ml that of a sensitivity and specificity (86.7% and 96.7%) respectively. There was a non-significant correlation between PCT levels and age, BMI, DM duration, HBAIC and HB%.ESR and CRP levels were positively correlated with PCT *(r*=0.727**, *P*=0.000) and *(r*=0.678 **, *P*=0.000) respectively. ESR levels were positively correlated with CRP *(r*=0.697**, *P*=0.000). **Conclusion:** PCT at a cut - off value 0.2 ng/ml is a sensitive and specific marker that can be used in the differentiation between Charcot arthropathy and OM. TLC count may be of limited value in differentiating OM and CN. The incorporation between PCT, ESR, CRP and MRI finding can help in differentiation between CN and OM.
[Sama Fathy Mohamed, Nashwa Mohamed Aboalnasr, Loai Mohamed El-Ahwal, Mamdouh Radwan El-Nahas, Saharmohey El-Din Hazza. **Serum Procalcitonine level in diabetic foot patients.** *Nat Sci* 2019;17(11):120-131]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 15. doi:10.7537/marsnsj171119.15.

Keyword: Diabetes, Charcot arthropathy (CN)**,** osteomyelitis (OM), Procalcitonine (PCT)

Introduction:

Diabetes represents an emerging global epidemic and one of the leading causes of morbidity and mortality. [(1)]Although many serious complications, such as kidney failure or blindness, can affect individuals with diabetes, it is the complications of foot that take the greatest toll. [(2)] Currently it can be estimated that millions of people are or will be affected by diabetic foot.[(1)]

It has been said that "every 30 seconds a limb is lost as a consequence of diabetes.[(3)]

Up to 66% of the persons admitted to the hospital with a diabetic foot infection have osteomyelitis.[(4)] its presence increases morbidity, risk of amputation and mortality. [(5),(6)]

Charcot neuro-osteoarthropathy is another devastating complication of diabetic peripheral neuropathy which can be another important cause of amputation.

The 5-year mortality rate after an amputation is more than 45 percent.[(1)] However that, it has been estimated that up to 85 percent of amputations occurring per year are preventable through early

detection of risky patient and early intervention in a skilled multidisciplinary foot care team.

In spite differentiation between CN and OM is often obvious, but it still difficult in many cases that may be need further investigations such MRI and Labeled Leucocyte Scan. Accuracy of MRI in diagnosing Charcot arthropathy versus Charcot arthropathy with osteomyelitis both in open or intact skin is extremely challenging. [7]

The role of PCT in differentiating several diabetic foot diseases is matter of discussion;

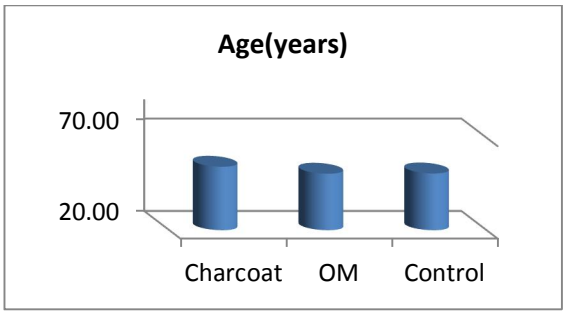


Fig (1) Age distribution of the studied groups.

2. Patients and Method:

Our study included 90 patients, acute Charcot group (30 patients) and acute osteomyelitis group (30 patients). 30 diabetic patients, all were recruited from Tanta and Mansoura university Hospital (diabetic foot clinic, diabetes outpatient clinics and inpatient wards) from October 2014 to April 2017; Diabetic state was confirmed or excluded according to the revised American Diabetes Association criteria (American Diabetes Association, 2014).[8] Ethical approval was obtained and each subject gave a written informed consent.

All patients in the study were subjected to:

- History taking
- Clinical examination:

1. General examination
2. Foot examination

- Assessment of possible peripheral arterial insufficiency.
- Assessment of possible PND
- Detection of site and stage of Charcot joint using imaging modalities (x - ray and MRI).
- Detection of DFO using probe to bone test and imaging modalities.
- Investigations:

Blood sampling was done for measuring FBG, HbA1c, CBC, serum creatinine, liver function tests, ESR and CRP as well as serum levels of Procalcitonine. We studied the role of the inflammatory markers (ESR, CRP, TLC and PCT) in the differentiation between the Charcot group and osteomyelitis group.

3. Results:

See **Fig (1).**

The mean age of patients in the Charcot group ***(54.3 ± 7.38 years)*** was not significantly different from either the OM or control groups ***(50.5 ± 10.89, 50.7 ± 10.85 years, respectively) (P= 0.249).***

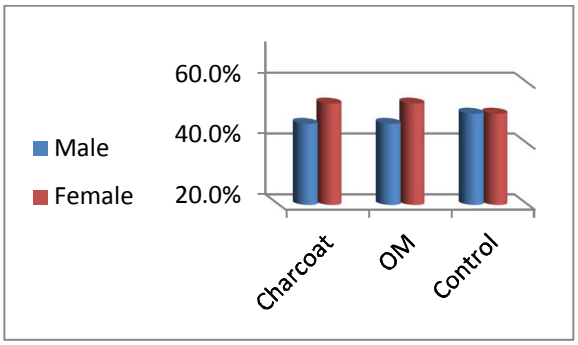


Fig (2) Gender distribution of the studied groups.

As regard gender, the Charcot group included 14 males ***(46.7%)*** and 16 females ***(53.3%).*** The OM group included 14 males ***(46.7%)*** and 16 females ***(53.3%),*** the control group included 15 males ***(50%)*** and 15 females ***(50%).*** The difference between all groups regarding gender was statistically insignificant ***(P= 0.956).***

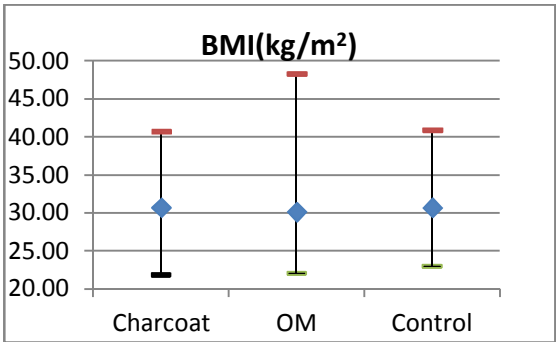


Fig (3) Difference between all groups as regard the body mass index.

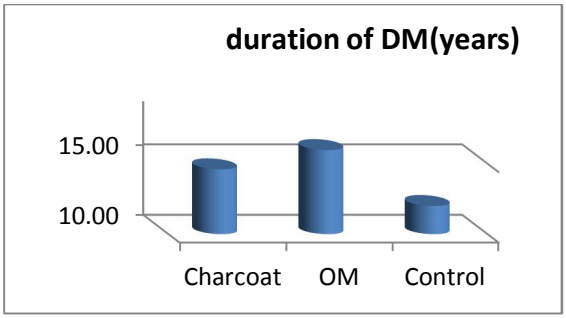


Fig (4) Diabetes duration in different groups

There was no significant difference between the studied groups as regard body mass index ***(P= 0.888)***.

Mean BMI in the studied groups was ***(30.68 ± 4.25, 30.10 ± 6.23 and 30.66 ± 5.02 kg/m2, respectively).***

Duration of diabetes was significantly higher in the Charcot and OM than in control groups with median ***(14.6, 15.9 and 12 years respectively). (P = 0.034)***

Metformin user was higher in the Charcot and control group ***[19(63.3%) and 13(43%)]*** respectively versus ***9(30%)*** in OM group which was of significant difference with ***(P= 0.033).***

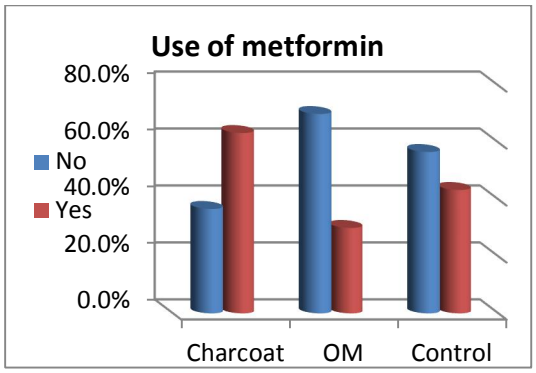


Fig (5) Use of metformin among the studied groups

Tab (1) Foot assessment:

Data		Groups				P
		Charcot		OM	Control	
ABI	Mean	1.09		1.0	1.05	0.017* A
	±SD	0.12		0.11	0.11	
VPT (Volts)	Median	33.8		34	18	0.000* A
	Range	22-49		25-49	5-29	
Doppler on pedal arteries	Monophasic	No	0	0	0	0.052 C
		%	0.0%	0.0%	0.0%	
	Biphasic	No	2	5	0	
		%	6.6%	16.7%	0.0%	
	Triphasic	No	28	25	30	
		%	93.3%	83.3%	100%	

Ankle/Brachial index (ABI) in the studied groups. There was significant difference ***(P= 0.017)*** between the OM and Charcot groups as regard the Ankle/Brachial index; Mean ABI was ***(1.09 ± 0.12, 1.0 ± 0.11 and 1.05 ± 0.11)***

Tab (2) Laboratory data of studied groups:

Data		Groups			P
		Charcot	OM	Control	
HbA1c (%)	Mean	10.09	9.36	8.80	0.001*
	±SD	1.42	1.29	1.17	
HB (gm/dl)	Mean	11.93	12.37	12.85	0.061
	±SD	1.67	1.30	1.43	
TLC (cu mm)	Mean	5423.4	11857	5386.6	0.144
	±SD	743.0	1798.2	860.5	
ESR (mm/hr)	Mean	16.9	55.2	10.0	0.000*
	±SD	8.51	23.6	4.11	
CRP (mg/l)	Mean	10.9	51.4	7.48	0.000*
	±SD	7.89	23.3	4.85	
Procalcitonine (ng/ml)	Mean	0.083	0.574	0.007	0.000*
	±SD	0.106	0.381	0.011	

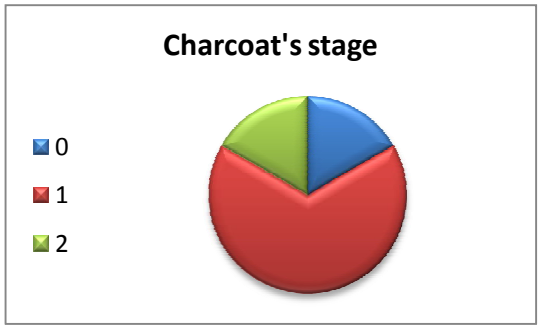
HbA1c levels were significantly different among Charcot and control group ***(P= 0.001)***. Mean level ***10.09 % ± 1.42*** and ***8.80 % ±1.17 respectively.***

Mean ESR was ***(16.9 ± 8.51, 55.2 ± 23.6 and 10.0 ± 4.11)*** in the three studied groups respectively.

ESR levels were significantly higher in the OM group in comparison to the Charcot and control group ***(P= 0.000)***, CRP levels were significantly higher in the OM group in comparison to the Charcot and control group ***(P= 0.000)***, Mean CRP was ***(10.9 ± 7.89, 51.4 ± 23.3 and 7.48 ± 4.85)*** in the three studied groups respectively.

Procalcitonine levels were significantly higher in the OM group in comparison to the Charcot and

control group ***(P= 0.000)***, Mean Procalcitonine was ***(0.083 ± 0.106, 0.574 ± 0.381 and 0.007 ± 0.011)*** in the three studied groups respectively.



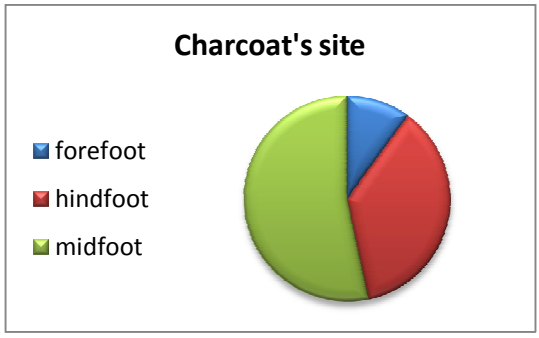


Fig (6, 7) Clinical characteristics of Charcot group.

Among Charcot group population there were ***5(16.7%)*** of patients belong to 0 stage, ***20(66.7%)*** stage 1 and ***5(16.7%)*** stage 2. Also ***3(10%)*** affected in forefoot, ***16(53.3%)*** in midfoot and ***11(36.7%)*** in hindfoot.

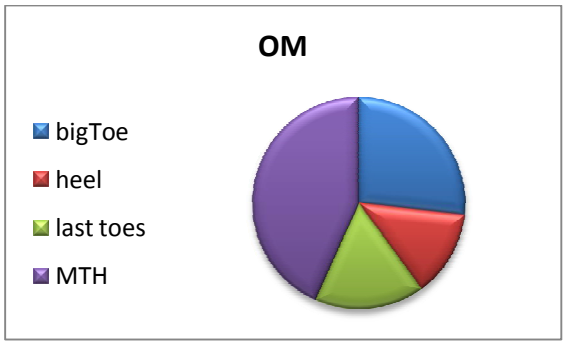


Fig (8) Different sites of foot OM in the studied group. MTHs, metatarsal heads.

The highest site of affection in osteomyelitic patients was MTH by 43%.

Tab (3) Comparison of Serum procalcitonine level, CRP, TLC and ESR in patient on different therapeutic modalities.

Data	TTT of DM				P
	Insulin		SU		
	Mean	±SD	Mean	±SD	
Procalcitonine	0.1949	0.27	0.2641	0.4266	0.616
CRP	23.05	22.42	23.64	28.22	0.6368
TLC	5805.4	1418.1	5242.8	801.56	0.0299*
ESR	27.70	23.48	26.91	26.88	0.4386

P: probability. Test used: Mann-Whitney U

There was no significant difference between patients on insulin and others on sulphonylureas as regard serum procalcitonine, CRP, ESR levels ***(P= 0.616, 0.6368 and 0.4386 respectively)***. TLC was significantly lower in diabetic subjects on sulphonylureas ***(P= 0.0299)***.

Tab (4) Comparative analysis of serum procalcitonine level, CRP, TLC and ESR in relation to presence or absent of systemic manifestation (fever) of the studied patient.

Data	Systemic manifestation (fever)				P
	Yes		No		
	Mean	±SD	Mean	±SD	
Procalcitonine	0.9049	0.35	0.1999	0.22	0.000*
CRP	70.54	18.98	22.34	19.29	0.000*
TLC	5545.5	5545.5	5718.4	1502.4	0.653
ESR	76.5	7.9	27.01	19.2	0.000*

Procalcitonine, **CRP** and **ESR** levels were lower in absence of fever than in presence of it and this difference was of high statistical significance among the studied patients ***(P= 0.000)*.** But there was no significant difference as regard **TLC** ***(P= 0.653)***.

Tab (5) Comparison of Serum procalcitonine level, TLC, ESR and CRP in relation to patients with HBA1C values <10 and others with values >10 of the studied patients.

Data	HBA1C				P
	<10		>10		
	Mean	±SD	Mean	±SD	
Procalcitonine	0.2158	0.3242	0.2460	0.4027	0.9276
CRP	24.15	24.24	19.77	26.85	0.1761
TLC	5569.4	1105.8	5655.7	1719.7	0.6974
ESR	26.71	24.67	30.11	25.40	0.2540

Kruskal Wallis Test

There was no significant difference in procalcitonine level, CRP, TLC and ESR among patients with different values of HBA1C. ***(P=0.9276, 0.1761, 0.6974 and0.2540 respectively).***

Tab (6) Comparison of Serum procalcitonine level, TLC, ESR and CRP in relation to patients with VPT values <25 and others with values >25 of the studied patients.

Data	VPT				P
	<25		>25		
	Mean	±SD	Mean	±SD	
Procalcitonine	0.0513	0.2054	0.3070	0.3613	0.000*
CRP	10.55	12.966	29.65	26.70	0.000*
TLC	5393.3	840.3	5683.3	1396.4	0.540
ESR	13.77	12.96	34.21	25.97	0.000*

Kruskal Wallis Test

There was significant difference in procalcitonine level, CRP and ESR among patients with different values of VPT. ***(P=0.000)*** and anon-significant difference as regard TLC ***(P=0.540)***.

Roc curve between infection (DFO) and serum procalcitonine, CRP, TLC and ESR.

Sensitivity, specificity, positive prediction, negative prediction and accuracy of serum level of PCT, CRP, ESR and TLC as diagnostic marker of infection.

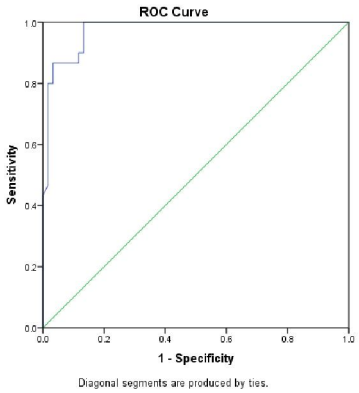
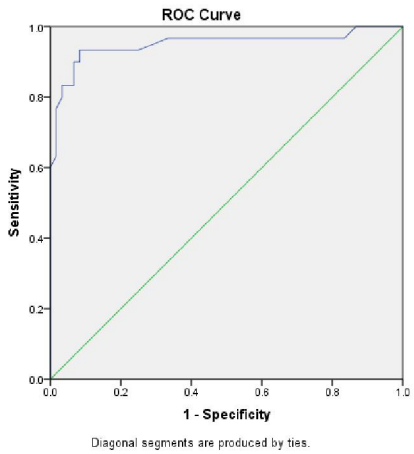


Fig (9) Roc curve of PCT to diagnose DFO.



Roc curve of ESR to diagnose DFO.

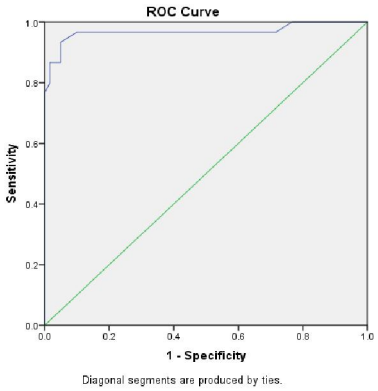


Fig (10) Roc curve of CRP to diagnose DFO.

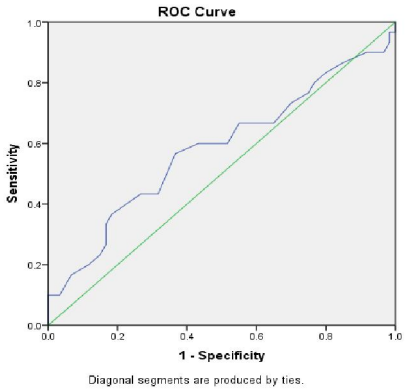


Fig (11) Roc curve of TLC to diagnose DFO.

Tab (7) Correlation between serums PCT, CRP, TLC, ESR levels

		PCT	CRP	ESR	TLC
PCT	r	1	0.678 **	0.727**	0.120
	p	.	0.000	0.000	0.261
CRP	r	0.678**	1	0.697**	0.166
	p	0.000	.	0.000	0.118
ESR	r	0.727**	0.697**	1	0.119
	p	0.000	0.000	.	0.118
TLC	r	0.120	0.166	0.119	1
	p	0.261	0.118	0.118	.

tailed

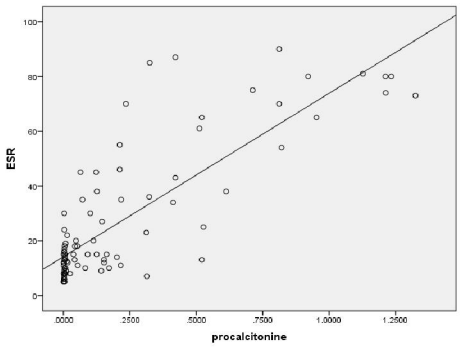
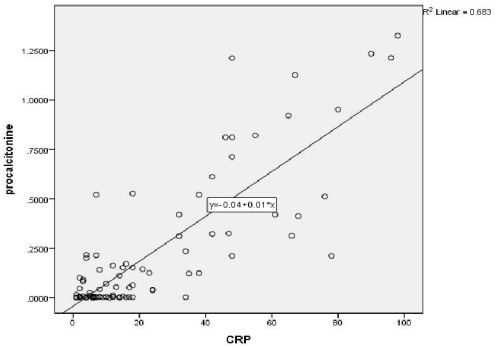


Fig (
PCT



vith

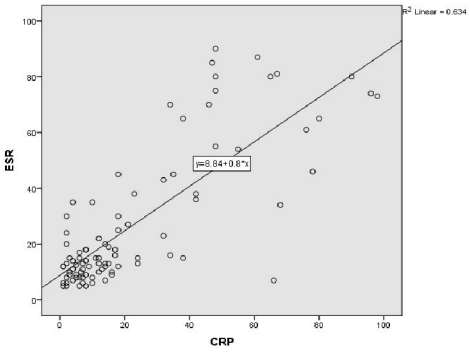


Fig (14) ESR levels were positively correlated with CRP (*r*=0.697**, *P*=0.000)

Tab (8) Correlation between serum PCT, ESR, CRP, TLC and different quantitative clinical and laboratory parameters of all subjects.

		PCT	CRP	TLC	ESR
Age	**r**	0.014	-0.005	0.634**	0.089
	P	0.895	0.961	0.000	0.406
BMI	**r**	0.022	-0.108	-0.268*	0.015
	P	0.833	0.309	0.011	0.891
DM duration	**r**	0.146	0.209*	0.285**	0.119
	P	0.170	0.048	0.007	0.263
HB	**r**	-0.093	0.061	0.0187	-0.152
	P	0.382	0.570	0.078	0.152
HBA1C	**r**	0.147	0.361	-0.008	0.220*
	P	0.166	0.737	0.941	0.038

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

ESR levels were positively correlated with HBA1C ***(r=0.220, P=0.038***) There was a non-significant correlation between plasma **ESR** levels and age, body mass index, DM duration and HB%**.**

There was a non-significant correlation between **CRP** levels and HBAIC, age, BMI and HB% and positive correlation with DM duration (r 0.209* P 0.048**).**

TLC levels were negatively correlated with BMI ***(r***-0.268***, P*** 0.011) There was a non-significant correlation with HBAIC and HB% and positive correlation with age and DM duration (r 0.634**P 0.000**) (r.** 0.285** **P** 0.007**).**

As regard **PCT** levels there was a non-significant correlation between PCT levels and age, BMI, DM duration, HBAIC and HB%.

4. Discussion

Diabetes represents an emerging global epidemic and one of the leading causes of morbidity and mortality.[1]According to data from IDF's Diabetes Atlas 2017, it is predicted that by 2045 there will be over 628.6 million people with diabetes in the world. It accounted that 10.7% of global all-cause mortality among people in (20-79 years) was due to diabetes. This is higher than the combined number of deaths from infectious diseases; AIDS, TB and malaria.[9]

Although many serious complications can affect individuals with diabetes, it is the complications of foot that take the greatest toll [2]. It has been said that "every 30 seconds a limb is lost as a consequence of diabetes.[3]

Up to 66% of the persons admitted to the hospital with a diabetic- foot infection have osteomyelitis. [4]

Charcot neuro-osteoarthropathy is another devastating and most destructive complication of diabetic peripheral neuropathy.

Morbidity and mortality rates become higher in those patients, as the 5-year mortality rate after an amputation is more than 45 percent.[1]

In spite differentiation between CN and OM is often obvious, but it still difficult in many cases that may be need further investigations such MRI and Labeled Leucocyte Scan. Accuracy of MRI in diagnosing Charcot arthropathy versus Charcot arthropathy with osteomyelitis extremely challenging,[7] especially when there is an open wound present. [10] Osteomyelitis through a hematogenous route can also occur in patients with both the acute and chronic Charcot arthropathy.[11]

So our chief concern is to find an accurate method that can helps in differentiation of several diabetic foot diseases for efficient management and better prognosis.

The role of PCT in differentiating several diabetic foot diseases is matter of discussion; the results published on its role are somewhat conflicting. In this study, we aimed to assess the value of PCT to distinguish acute osteomyelitis from acute Charcot arthropathy. Since PCT is considered an acute phase protein.[12]a group of diabetic patients without foot complication was enrolled, to exclude the inflammatory process accompanying diabetes that may cause an increase of PCT concentration.

Analysis of the clinical results of the present work revealed that there was no significant difference among our patients groups regarding age, gender and BMI, these results are in agreement with ***Younis et al.*** [14] ***and Van Asten et al.*** [14] who revealed that age and gender had no influence on prevalence of CN and OM. But on the other hand to ***Cunha et al.***[15] ***and Huang et al.*** [16] that demonstrated that OM is the second cause of infection in elderly and associated with increased the long-term mortality in them, particularly in the males.

Comparisons between different groups regarding duration of diabetes were of significant value as we found that complications of diabetes are strongly related to duration of disease this is in agreement to ***Younis et al 2015 and Chawla et al*** [17]

Metformin user was significantly lower in OM group (30%) versus Charcot and control group and this may be due to the more insulin users in this group. Our result is in agreement with ***Xiyan et al 2015*** who revealed that metformin improves diabetic bone health by rebalancing catabolism and nitrogen disposal**.**

Marupuru et al 2017 revealed that there is a Protective effect to metformin against tuberculosis infections in diabetic patients so may be have same protection against OM but this need further studies. [18]

HBAIC was significantly higher among Charcot's patient and this is in agreement to ***Younis et al 2015*** as the higher HBA1C is associated with presence of micro and macrovascular complications. [19]

All patients in the Charcot and OM groups had loss of protective sensation by VPT which was significantly different ***(P< 0.001)*** from other patients in the control group [33.8, 34 versus 18 Volts respectively]. This Suggest that neuropathy and loss of protective sensation is an important risk factor of diabetic foot diseases included osteomyelitis. [20]

We found that midfoot was the most common site of affection among Charcot's patients this in agreement to ***Silvampatti et al. 2016.*** This is due to equinus contracture and motor neuropathy. [21]

Stage 1 was the most common presentation among Charcot's patients in our study this may be due to the presence of redness, hotness and swelling that makes patient worry to seek medical advice.

MTH (43.3%) was the most common site of affection in osteomyelitic patients followed by big toe (26.7%) and last toe (16.7%) then heel (13.3%). ***Giurato et al 2017*** documented that osteomyelitis can affect any bone but most frequently the forefoot (90%). [22]

TLC showed nonsignificant difference between study groups. Results of our study are in agreement to ***Nina et al 2007 and Schwegler et al 2008 and Giurato et al 2017*** that revealed that TLC of limited sensitivity for the diagnosis of osteomyelitis.[23][24] And in contrast to ***Kishner S 2016*** who revealed that Leukocytosis is common in acute osteomyelitis before therapy.

Our results regarding to TLC in acute Charcot also supported by ***Kucera et al. 2016*** who revealed that laboratory readings of TLC in Charcot do not show higher results. [25]

In acute Charcot there is dissociation between presence of signs of inflammation by increased skin temperature and the lack of systemic response.[23]

Our result can be explained as diabetic patients have been demonstrated to have defects in leukocyte chemotaxis, diapedesis, and phagocytosis. These cellular abnormalities may be an underlying factor in diminished inflammatory responses sometimes observed in foot infections in those patients. Measurement of the white blood cell count may not help distinguish Charcot changes from osteomyelitis.[26]

TLC was not significantly different in patient with or without fever. Our result in agreement to ***Catherine et al 2009***. The diabetic patient has an altered immune response to infection, as hyperglycemia allows bacteria to replicate at an increased rate and causes defects in leukocyte function.[27]

We found that TLC levels were positively correlated with age in agreement the ***NHANES study 2004 and Nilsson et al. 2014*** explaining that can be due to sex difference in TLC among different age group.[28] On the other hand to ***Aminzadeh and Parsa 2011*** that revealed that TLC readings were slightly decreased in old age.[29]

TLC was significantly higher in diabetic subjects on insulin therapy. The majority of our patients were type 2 DM and most of them were on insulin therapy that is related to the long duration of diabetes in those patients that by its rule related to the micro and macrovascular complications of DM. ***Chung, et al 2005*** *and* ***Tong et al 2004*** reported that elevated WBC count, even within the normal range, is associated with both macro- and microvascular complications in type 2 diabetes. Chronic inflammation, as indicated by a higher TLC count, may play a linkage role in the development of macro- and microvascular complications in diabetes.[30]

We found a positive correlation between TLC and HBAIC this is in agreement to ***Borne et al 2016.*** It has already been demonstrated that insulin resistance (IR) that associated with elevated HBA1C is associated with the stimulation of erythroid progenitors RBC and WBC count and with increased levels of inflammation markers. [31-33]

Also there was positive correlation between TLC and VPT this in agreement to ***Moursy EY, Helmy M, et al 2015***. Previous epidemiological studies have highlighted that chronic low grade inflammation is associated with diabetes mellitus. [34][35] Peripheral diabetic neuropathy is associated with increased biochemical markers of inflammation and endothelial dysfunction. [36]

The sensitivity and specificity for the diagnosis of osteomyelitis via TLC (cutoff value >5550) was 56.7and 63.3 respectively. Previous study by ***Michail et al 2013*** revealed that the sensitivity and specificity were (cutoff value >14 × 10(9)/L) 75% and 79% respectively.[37]On the other hand to ***Joseph et al 2008*** revealed that the white blood cell count is often normal in the setting of acute osteomyelitis.[38] While

some research has highlighted the potential utility of the WBC differential in the diagnosis of foot infection. [39]

We found that values of ESR were significantly higher in OM group as compared to Charcot and control groups. This in agreement to ***Nina L. Petrova, et al 2007, Tomas, et al 2016***. The later revealed that ESR in CN does not show higher values.

The mean values in OM group were 55.2±23.6 mm/h and in Charcot group were 16.9±8.51mm/h. another study found that the mean ESR in patients with osteomyelitis was only 47.6 (±13) mm/h. [40] Previous study showed that mean ESR in acute Charcot was 22 mm/h with range (13-36)mm/h.

We found that cut off value of ESR to diagnose acute OM was 22.50 mm/hr that was of sensitivity and specificity 93.3% and 91.7 respectively.

Based on a study by ***Butalia et al 2008***, an ESR > 70 mm/hr significantly increases the probability of OM. ***Michail et al 2013*** ESR (cutoff value >67 mm/h) of sensitivity and specificity 84% and 75% respectively .[41] ***Abolfotouh 2011*** revealed ESR level (54 mm/hr) of 85% sensitivity, 70% specificity to predict DF.[42]Others reported that osteomyelitis was 12 times more likely in suspected cases if the ESR exceeded 40 mm/h [43]. ***Laura, et al 2017 and Fleischer A, et al 2009.*** revealed that ESR > 60 mm/h are significantly predictive of DFO. [44]

Also there was a significant positive correlation between HBA1C and ESR *P=0.038* this is in agreement with ***Samocha-Bonet et al 2003***[45] There are studies reporting a positive correlation between RBC aggregation and HbA1c level, the enhanced RBC aggregation in these patients is probably due to plasma protein changes caused by infection or inflammation, and associated with the elevated plasma fibrinogen level which is known to be a primary determinant of RBC aggregation and was more highly correlated than other parameters with ESR.[46]

We found that CRP values were significantly higher in OM group in comparison to Charcot and control groups with mean values in OM group 51.4 ± 23.3 mg/l and 10.9 ± 7.89 mg/l in Charcot group. This supported by ***Tomas et al 2016*** and ***Nina l. Petrova, et al 2007*** CRP is one of the most sensitive markers of inflammation that used in practice as direct serological measure of acute phase response to injury and infection the local inflammatory response seen in our patients of Charcot may be related to increased inflammatory cytokines but this did not lead to a classical systemic acute phase response.

High sensitive CRP may be superior to CRP in acute Charcot. It can be used in apparently healthy people. It measures CRP in the range from 0.5 to 10 mg/L. The CRP test is ordered to evaluate people who have signs and symptoms of a serious bacterial infection or of a serious chronic inflammatory disease such as rheumatoid arthritis. It measures CRP in the range from 10 to 1000 mg/L. N. L. Petrova, T. K. Dew, et al 2015 reported that at presentation of disease (acute Charcot) the high-sensitivity CRP was significantly higher in patient of acute Charcot than in people with and without diabetes but they pointed to that it not significantly differ from the presentation and resolving of the disease.[47] In the other hand ***Jemmott, et al 2008*** added that high sensitivity CRP can be also used in monitoring disease activity in acute Charcot.[48]

There was positive correlation between CRP and VPT this in agreement to ***Doupis, et al 2009.*** Peripheral diabetic neuropathy is associated with increased biochemical markers of inflammation.

DM duration and CRP levels were positively correlation in our study. this in agreement with ***Azenabor et al 2011*** and ***Chung et al 2005*** they concluded that acute phase reactant level increase with long duration of DM and associated with microvascular complications. Subclinical inflammation in these patients may therefore be partly due to activation of the inflammatory response by advanced glycation end products.[49][50]

We found that the cutoff value of CRP in diagnosis of acute OM was 19.5 mg/l that of sensitivity 93.5% and specificity 95%. ***Michail et al 2013*** cutoff value >14 mg/L were of 85% sensitivity and 83% specificity.[37] The results of the present study showed that serum Procalcitonine levels were significantly higher in the OM group in comparison to the Charcot and control group ***(P< 0.001)***, Mean Procalcitonine was ***(0.083 ± 0.106, 0.574 ± 0.381 and 0.007 ± 0.011)*** in the three studied groups; Charcot, OM and Control group respectively. This is in agreement to ***et al 2013, Tomas 2016, Taywade et al 2016***.

Serum levels of Procalcitonin are very low in healthy individuals (< 0.1 ng/ml) and increases rapidly in response to bacterial endotoxin. These properties together with a half-life of 22 to 29 hours have made Procalcitonin, a convenient tool to monitor serious infections and to discriminate bacterial infections from viral and non-infective inflammatory conditions.

Previous study showed that Procalcitonin could be a potential useful biomarker to diagnose acute bacterial septic arthritis. The level of procalcitonin can be obtained promptly and thus, it could be used along with other clinical information to differentiate between acute bacterial septic arthritis and acute inflammatory non-septic arthritis before the result of synovial culture can be obtained. [51]

In the other hand to our result ***Fleischer et al 2017*** revealed that PCT did not reach statistical

significance when comparing patients with OM and patients without bone infection.(52)(53)

We determined a best cut-off value of PCT to diagnose a case of acute OM was **0.2 ng/ml** that of a sensitivity and specificity (**86.7%** and **96.7%)** respectively. ***Maharajan et al., 2016*** documented that a cutoff of 0.4ng/ml, is a sensitive and specific marker in the diagnosis of Septic Arthritis and Acute Osteomyelitis. ***E Greeff 2012*** revealed the cut off value was 0.2ng/mL with sensitivity 91% and specificity 82%. (54) ***Fottner et al 2007*** and ***Taywade et al 2016*** had cut off level of 0.5ng/ml. ***Michail, et al 2013*** revealed cutoff value >0.30 ng/mL of sensitivity and specificity 81% and 71% respectively. This reflects the absence of a general consensus in deciding the cut-off.

Previous study to the diagnostic performance of serum procalcitonin in the identification of osteomyelitis and septic arthritis was investigated in patients who presented with fever. It was reported that the lower cut-off value of 0.2-0.3 ng/mL improved the sensitivity to 90% and suggested that the lower cut-off should be used for localized infection such as septic arthritis.(55)

If we use other cutoff point rather than 0.2ng/ml we will have lower sensitivity results. The objective in an infection marker is high sensitivity, otherwise patients with true infection who need antibiotic treatment may be missed.

The results revealed that PCT, among all the inflammatory markers (ESR, TLC and CRP) have the highest area under the curve (0.974, 0.950, 0.581 and 0.968 respectively) and the greatest specificity among them for diagnosing DFO (96.7, 91.7, 63.3 and 95% respectively) this is in agreement with ***Christ-Crain et al 2008***. ***Anurag Markanday 2015*** Procalcitonin has an advantage over CRP and ESR due to its better specificity and it is the best correlated with infection.(56)

There was positive correlation between PCT and VPT. Previous epidemiological studies have highlighted that chronic low grade inflammation is associated with diabetes mellitus. (34)(35) Peripheral diabetic neuropathy is associated with increased biochemical markers of inflammation and endothelial dysfunction. (36)

PCT showed higher values in patients with fever and that was of significant value with *P value 0.000.* Previous study revealed that normally, PCT does not increase when local bacterial infection occurs unless the infection is accompanied by systemic inflammatory reactions.(57)

We found positive correlation between ESR, CRP and PCT *(P*<0.001). This is in agreement to ***Zhang [1], et al 2014*** and ***Kotulska, et al 2015*** and ***Rui-Ying Xu, Hua-Wei Liu, et al 2014.*** (58)(59) Our study revealed thatno correlation between TLC and PCT this in agreement to ***Abedini, et al 2012 and*** in contrast to ***Magrini et al 2014*** who revealed that there were a direct correlation between PCT and TLC.(60)(61)

Conclusion:

PCT at a cut - off value 0.2 ng/ml is a sensitive and specific marker that can be used in the differentiation between Charcot arthropathy and DFO.

Serum Procalcitonin may be used as a new diagnostic marker for initiation of treatment in the management of Acute DFO.

Elevated TLC count, even within the normal range, is associated with both macro and microvascular complications of diabetes. TLC count may be of limited value in differentiating DFO and CN.

The incorporation between PCT, ESR, CRP and MRI finding can help in differentiation between CN and DFO.

In acute Charcot there is dissociation between presence of signs of inflammation by increased skin temperature and the lack of systemic response.

Reference:

1. Ibrahim A. IDF Clinical Guidelines on the Diabetic Foot: a guide for health professionals. Diabetes Voice. 2017.
2. Lanka S. Step by Step, improving diabetic foot care in the developing world. Practical diabetes. 2006;23(8):1–6.
3. Hayes C KA. Role of physical activity in diabetes management and prevention. J Am Diet Assoc. 2008 ;108(4 Suppl 1):S19-23.
4. Hartemann-Heurtier A. SE. Diabetic foot osteomyelitis. Diabetes Metab,. 2008;34(2):87–95.
5. Price PP, Armstrong PD, Moffatt PC, et al. Guest editorial: are diabetes-related wounds and amputations worse than cancer ?Int Wound J.2007;4(4):286–7.
6. Ertugrul BM, Oncul O, Tulek N, et al. A prospective, multi-center study : factors related to the management of diabetic foot infections. Eur J Clin Microbiol Infect Dis. 2012;31:2345–52.
7. Malhotra R, Shu-Yi Chan C, Nather A. Osteomyelitis in the diabetic foot. Diabetic Foot and Ankle. 2014; 31:113–16.
8. American diadetes Association. Standards of Medical Care in Diabetesd 2014. Diabetes Care. 2014;37(1):S14–80.
9. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017.
10. Rubin LG. Osteomyelitis Associated with

Charcot Arthropathy, Osteomyelitis of the Foot and Ankle. 2015;4: 157-165.
11. Ramanujam CL, Stapleton JJ ZT. Diabetic Charcot neuroarthropathy of the foot and ankle with osteomyelitis. Clin Pod Med Surg. 2014;31:487–92.
12. Uzun G, Solmazgul E, Curuksulu H, et al. Procalcitonin as a diagnostic aid in diabetic foot infections. Tohoku J Exp Med. 2007;213(4):305–12.
13. Van Asten SA, La Fontaine J, Peters EJ. The microbiome of diabetic foot osteomyelitis. Eur J Clin Microbiol Infect Dis. 2016;35:293–8.
14. Younis BB, Shahid RA. Charcot osteoarthropathy in type 2 diabetes persons presenting to specialist diabetes clinic at a tertiary care hospital. BMC Endocr Disord. 2015;15: 28.
15. Cunha BA. Osteomyelitis in elderly patients. Clin Infect Dis. 2002;35(3):287–93.
16. Huang CC, Tsai KT, Weng SF et al. Chronic osteomyelitis increases long-term mortality risk in the elderly: a nationwide population-based cohort study. BMC Geriatr.2016:16: 72.
17. Chawla A, Chawla R, Jaggi SH. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum?. Indian Journal of Endocrinology and Metabolism. 2016; 20:246:51.
18. Marupurua S, Senapatia P, Pathadkaa S. Protective effect of metformin against tuberculosis infections in diabetic patients: an observational study of south Indian tertiary healthcare facility. Braz J Infect Dis. 2017;21(3).
19. Aastha Chawla, Rajeev Chawla and SJ. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016;20(4):546–551.
20. Hannan CM. Special Considerations in the Management of Osteomyelitis Defects (Diabetes, the Ischemic or Dysvascular Bed, and Irradiation). Osteomyelitist. 2009;23(2):132–40.
21. Silvampatti S, Nagaraja HS, Rajasekran S. Midfoot charcotarthropathy: overview and surgical management. J foot ankle surg.
22. Giurato L, Meloni M. Osteomyelitis in diabetic foot: A comprehensive overview. World J Diabetes. 2017;8(4):135–42.
23. Petrova NL, Moniz C, Elias DA et al. Is there is systemic inflammatory response in the acute charcot foot? Diabet Care.2007;30:977–80.
24. Boutin RD, Brossmann J, Sartoris DJ, et al. Update on imaging of orthopedic infec- tions. Orthop Clin North Am. 1998;29:41–66.
25. Kucera T, Shaikh HH SP. Charcot Neuropathic Arthropathy of the Foot: A Literature Review and Single-Center Experience. J Diabetes Res. 2016;3207043.
26. Todd C, Sommer D et al. Charcot Foot: The Diagnostic Dilemma. Am Fam Physician. 2001;64(9):1591–8.
27. Bamberger M, Daus D. Osteomyelitis in the feet of diabetic patients. Long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. Am J Med. 1987; 83:653–60.
28. Cheng J. Chan G. Cembrowski S et al. "Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race,." Lab Hematol pp. 2004;10(1):42–53,.
29. Aminzadeh Z. Relationship between Age and Peripheral White Blood Cell Count in Patients with Sepsis. Int J Prev Med. 2011;2(4):238–42.
30. Chung FM, Tsai JC, Chang DM et al. Peripheral total and differential leukocyte count in diabetic nephropathy: the relationship of plasma leptin to leukocytosis. Diabetes Care.2005; 28:1710–7.
31. Yan Borné J, Gustav Smith PMN. Total and Differential Leukocyte Counts in Relation to Incidence of Diabetes Mellitus: A Prospective Population-Based Cohort Study. PLoS One. 2016;11(2):e0148963.
32. Biadgo B, Melku M, Abebe SM et al. Hematological indices and their correlation with fasting blood glucose level and anthropometric measurements in type 2 diabetes mellitus patients in Gondar, Northwest Ethiopia. Diabetes Metab Syndr Obes. 2016;9:91–99.
33. Borné Y, Smith JG, Nilsson PM et al. Total and Differential Leukocyte Counts in Relation to Incidence of Diabetes Mellitus: A Prospective Population-Based Cohort Study. journal. pone; 2016;11:1-18.
34. Moursy EY, Megallaa MH, Mouftah RF, et al. Relationship Between Neutrophil-Lymphocyte Ratio and Microvascular Complications in Egyptian Patients with Type 2 Diabetes. Am J Intern Med. 2015;3:250–5.
35. Pitsavos C, Tampourlou M, Panagiotakos DB et al. Association Between Low Grade Systemic Inflammation and Type 2 Diabetes Mellitus Among Men and Women from the ATTICA Study. Stud. Rev Diabet. 2007;4(2):98–104.
36. John D, Thomas E, Lyons SW. Microvascular Reactivity and Inflammatory Cytokines in Painful and Painless Peripheral Diabetic Neuropathy. J Clin Endocrinol Metab. 2009;94(6):2157–2163.
37. Michail M, Jude E, Liaskos C et al. The performance of serum inflammatory markers for the diagnosis and follow-up of patients with

osteomyelitis. Int J Low Extrem Wounds. 2013;12:94–9.
38. Fritz JM, McDonald JR, et al. Osteomyelitis: Approach to Diagnosis and Treatment. Phys Sportsmed. 2008; 36:1-9.
39. Armstrong DG, Lavery LA, Sariaya M AH. Leukocytosis is a poor indicator of acute osteomyelitis of the foot in diabetes mellitus. J Foot Ankle Surg. 1996;35(4):280–3.
40. Lipsky BA. Osteomyelitis of the foot in diabetic patients. Clin Infect Dis. 1997;25:1318–2.
41. Butalia S, Palda VA, Sargeant RJ, et al. Does this patient with diabetes have osteomyelitis of the lower extremity?. ; JAMA. 2008; 299:806-13.
42. Abolfotouh MA, Alfaifi SA, Al-Gannas AS. Risk factors of diabetic foot in central Saudi Arabia. Saudi Med J. 2011;32:708-13.
43. Lipsky A. Controversies in Diagnosing and Managing Osteomyelitis of the Foot in Diabetes. Clin Infect Dis. 2004;39(2):S115–S122.
44. Fleischer AE, Didyk AA, Woods JB et al. Combined Clinical and Laboratory Testing Improves Diagnostic Accuracy for Osteomyelitis in the Diabetic Foot. J Foot Ankle Surg; 2009; 48: 39–46.
45. Samocha-Bonet D, Lichtenberg D TA. Enhanced erythrocyte adhesiveness/aggregation in obesity corresponds to low-grade inflammation. Obes Res. 2003;11(3):403–7.
46. Shaoying Ye, Ping Ruan JY. The impact of the HbA1c level of type 2 diabetics on the structure of haemoglobin. Sci Rep. 2016;6: 333-52.
47. Petrova NL, Dew TK. Inflammatory and bone turnover markers in a cross-sectional and prospective study of acute Charcot osteoarthropathy. Diabet Med. 2015;32(2):267–73.
48. Jemmott T, Bates M, Petrova NL. Proinflammatory cytokines and high sensitivity C-reactive protein to monitor disease activity in acute Charcot feet. In: DFSG 2008, Lucca, Italy, 11-14 September. 2008.
49. Azenabor A, Ogbera AO, Adejumo NE et al. Acute phase reactant dynamics and incidence of microvascular dysfunctions in type 2 diabetes mellitus. J Res Med Sci; 2011;16:1298–1305.
50. Chung FM, Tsai J. CR, Chang DM et al. Peripheral Total and Differential Leukocyte Count in Diabetic Nephropathy. Diabetes Care. 2005;28:1710–7.
51. Paosong S, Narongroeknawin P, Pakchotanon R. Serum procalcitonin as a diagnostic aid in patients with acute bacterial septic arthritis Authors. Int J Rheum Dis. 2015;18(3):352–9.
52. Maharajan K, Patro DK, Menon J et al. Serum Procalcitonin is a sensitive and specific marker in the diagnosis of septic arthritis and acute osteomyelitis. J Orthop Surg Res; 2013;8:19.
53. Mutluoğlu M, Uzun G, İpcioğlu OM et al. Can procalcitonin predict bone infection in people with diabetes with infected foot ulcers? A pilot study. Pract; Diabetes Res Clin. 2011;94:53-6.
54. Greeff E. Is procalcitonin useful in diagnosing septic arthritis and osteomyelitis in children?. SA orthop. 2012;11:1.
55. Shen CJ, Wu MS LKh. The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2013;32:807–14.
56. Markanday A. Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. Open Forum Infect Dis. 2015;2(3):ofv098.
57. Whang KT, Steinwald PM, White JC, et al. Serum calcitonin precursors in sepsis and systemic inflammation. J Clin Endocrinol Metab. 1998;83:3296–3301.
58. Kotulska A, Kopeć-Mędrek M, Grosicka A et al. Correlation between erythrocyte sedimentation rate and C-reactive protein level in patients with rheumatic diseases. Reumatologia. 2015;53:243–6.
59. Rui-Ying Xu, Hua-Wei, Liu J-LL. correlation Procalcitonin and C-reactive protein in urinary tract infection diagnosis. BMC Urol. 2014;14:45.
60. Abedini M, Delpisheh A, Nikkhu B et al. Procalcitonin and white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) alterations in children with systemic inflammatory response syndrome before and after treatment. AFR J BIOTECH; 2012;11:10989–93.
61. Magrini L, Gagliano G, Travaglino F et al. Comparison between white blood cell count, procalcitonin and C reactive protein as diagnostic and prognostic biomarkers of infection or sepsis in patients presenting to emergency department. ClinChem Lab Med; 2014;14:1–8.

8/7/2019