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Detection Of Procalcitonin, Vitamin D3 Levels, And Many Physiological Parameters As Early Indicators For Foot Diabetic Diagnosis In Kirkuk City

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Abstract
This study aimed to evaluate the relationship between procalcitonin and vitamin D3 levels, as well as various physiological parameters, to identify early indicators for the diagnosis of diabetic foot disease in Kirkuk city. Diabetic foot disease is a common and serious complication of diabetes, which can lead to tissue damage and severe inflammation, potentially leading to amputation if not diagnosed and treated in a timely manner. The study focused on measuring procalcitonin (PCT), a protein used as a biomarker for bacterial infections, as well as vitamin D3, which is essential for bone health and immune function, and osteopontin (OPN), a secreted phosphoprotein involved in numerous biological activities and plays a role in bone metabolism and homeostasis. Additionally, several physiological parameters, including blood sugar, cholesterol levels, and other relevant indicators, were examined for their potential association with the development of diabetic foot disease.
Keywords: *Procalcitonin , Vitamin D3 , Osteopontin , Diabetic Foot Ulcers , Diabetes Mellitus*

List of Abbreviations
25-hydroxyvitamin D (25(OH)D)
Blood Urea(B.Urea)
Diabetes Mellites (DM)
Infected Diabetic Foot Ulcer (IDFU)
Diabetic Foot Ulcer (DFU)
Enzyme Linked Immunosorbent Assay (ELISA)
Fasting Blood Sugar (FBS)
Glycosylated Hemoglobin (HbA1c)
High-Density Lipoprotein (HDL)
Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
Infection Diabetic Foot Ulcer (IDFU)
Low-Density Lipoprotein (LDL)
Osteopontin (OPN)
Procalcitonin (PCT)
Receiver Operating Characteristics (ROC)
Serum Creatinine (S.Cr)
Total Cholesterol (TC)
Triglycerides (TG)
Type II Diabetes Mellitus (T2DM)
Very Low-Density Lipoprotein (vLDL)

INTRODUCTION

Diabetic foot ulcers are a serious complication of diabetes, posing significant health risks and contributing significantly to deaths and morbidity worldwide. (Akkus, and Sert, 2022). The International Diabetic Foot Working Group defines diabetic foot as an infection, ulcer, or tissue damage to the foot, often associated with neuropathy and/or peripheral arterial disease (PAD) in the lower extremities, in a person

with diabetes or a clinical history of the condition. According to the International Diabetes Federation, approximately 540 million adults worldwide have diabetes, and this number is expected to rise to 783 million by 2045, a 46% increase. Furthermore, a person with diabetes has a 34% lifetime risk of developing a diabetic foot ulcer (DFU) (Liu *et al.*, 2024).Diagnostic biomarkers have been successfully applied in many areas of medicine. However, early diagnosis of bacterial infections remains a challenge. Of the many proposed markers of sepsis and infection, PCT is the most well-evaluated. This marker may help physicians diagnose early and assess the severity of systemic inflammation resulting from bacterial infections. (Lee, 2013). Procalcitonin (PCT), a polypeptide secreted by thyroid C cells, liver, lung, and kidney parenchyma cells, consists of 116 amino acids and serves as a precursor to calcitonin, which plays an important role in the diagnosis of bacterial infections as a biomarker. reported that PCT may be a key indicator for the prognosis of IDFU patients. (Wang *et al.*, 2021).Several factors suggest a close relationship between vitamin D and diabetic foot ulcers. Research suggests that vitamin D plays a role in stimulating the production of antimicrobial peptides, which can speed up the healing process in diabetic foot ulcers. Furthermore, vitamin D acts as an inhibitor of bacterial biofilm formation, and a deficiency can increase the risk of infection. Low vitamin D levels have been associated with elevated pro-inflammatory cytokines and inflammatory markers in individuals with diabetic foot ulcers. (Iqhrammullah *et al.*, 2024). Vitamin D is a versatile steroid hormone that plays a key role in calcium and phosphorus metabolism, as well as regulating bone life cycles. It is also involved in various processes, including the inflammatory response, immune system function, and cell cycle regulation. Furthermore, many chronic diseases, such as diabetes and its complications, are associated with vitamin D levels. (Tang *et al.*, 2022). Typically, vitamin D status can be evaluated by measuring the level of serum 25-hydroxy-vitamin D. (Ali, 2019)Osteopontin (OPN), a secreted phosphoprotein, is a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family of cell matrix proteins and participates in many biological activities. Studies have shown that OPN plays a role in bone metabolism and homeostasis. OPN has been demonstrated to be closely related to the occurrence and development of many bone-related diseases, such as osteoporosis, rheumatoid arthritis, and osteosarcoma. (Si *et al.*, 2020).

MATERIAL AND METHODS

Ethics approval

All participants were recruited from Kirkuk Teaching Hospital, Kirkuk General Hospital, as well as several laboratories and clinics, during the period from November 2024 to February 2025. The ages of the participants ranged between 40 and 80 years across all study groups.

Study population:

The study population was divided into four groups: Control Group: This group consisted of 25 healthy nondiabetic individuals. Diabetes Mellitus (DM) Group: This group included 25 patients with type 2 diabetes mellitus (T2DM) who did not have any foot complications. Diabetic Foot Ulcer (DFU) Group: This group comprised 25 participants with diabetic foot ulcers in the early stage without clinical signs of infection. Infected Diabetic Foot Ulcer (IDFU) Group: This group included 25 participants with diabetic foot ulcers in the late stage with infection. All diabetic patients included in this study were diagnosed by an endocrinologist based on clinical evaluations and measurements of fasting blood sugar (FBS) and glycated hemoglobin (HbA1c).The classification of patients with diabetic foot ulcers was based on the criteria set by the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF). Specifically, the Wagner classification system was used to assess ulcer severity, which categorizes ulcers based on depth and the presence of osteomyelitis or gangrene as follows: (Grade 0: Pre- or post-ulcerative lesion, Grade 1: Partial or full-thickness ulcer, Grade 2: Ulcer probing to tendon or capsule, Grade 3: Deep ulcer with osteitis, Grade 4: Partial foot gangrene, Grade 5: Whole foot gangrene) IDFU group (2, 3, 4, and 5 Wagner grades) and DFU group (0 and 1 Wagner grades)Clinical signs of infection recorded in this study included redness, wound swelling, pus discharge or exudates, fever, and localized pain in the infected area (Al-Shammaree *et al.*, 2017).

Specimen collection:
(5 ml) of peripheral venous blood was withdrawn from each patient using a sterile syringe. Information was taken from the patient, such as name, age, duration of diabetes, presence of other diseases, and family history of diabetes. The patient's height and weight were also measured, as well as diastolic and systolic blood pressure. After withdrawing the blood sample, the sample was divided into:

- Part One: Place (4 ml) in sterile, dry plastic tubes, leaving them for 10 minutes at room temperature. After that, the serum was separated by a centrifuge at 3000 rpm for 10 minutes. Then, the serum was placed in Eppendorf tubes and stored at (-20 °C) until used for biochemical tests.
- Part Two: (1 ml) of blood was placed in tubes containing anticoagulant materials. The EDTA tube was used to conduct direct tests such as FBS and HbA1C tests.

Measurements of Lipid profile and Renal Function
Lipid profile (total cholesterol, triglyceride, high-density-lipoprotein-cholesterol and Renal Function Tests (urea, creatinine,) were measured using autoanalyzer device (SMART-150, USA). Low-density lipoprotein-cholesterol [LDL-C] and Very Low-Density Lipoprotein [VLDL]) were calculated using Friedewald'sequation (Friedewald et al., 1972).

Measurements of Diabetes profile
to mesure the HbA1C (using a commercial kit, Boditech Med Inc, South Korea), and FBS (using a commercial kit ,Roche Diabetic Care, Germany).

Measurements of Bone Health
Bone Health (Phosphor and calcium) ,were measured using autoanalyzer device (SMART-150, USA).

Detection of PCT , vitamin D and OPN by Enzyme-Linked Immunosorbent Assay (ELISA):
Blood plasma was used for PCT estimation, using Human PCT ELISA kit (Bioassay Technology Laboratory , china) with a sensitivity limit <2.49 pg/ml and standard curve range (5–20000) pg/ml.and to estmaited vitamin D using Human 25-dihydroxy vitamin D ELISA kit (Bioassay Technology Labortory ,china) with a sensitivity limit <0.23 ng/ml and range (0.5–150) ng/ml, and to estmaited OPN using Human Osteopontin ELISA Kit (Bioassay Technology Labortory , china) with a sensitivity limit < 0.15 ng/ml and range (0.3–90) ng/ml.

Data analysis Statistical analysis was conducted using SPSS software version 26. Continuous variables were expressed as the mean ± standard deviation. The Kolmogorov-Smirnov test was employed to assess the normality of the data. Comparisons of all parameters between groups were analyzed using ANOVA. The area under the curve (AUC) was measured to evaluate diagnostic accuracy. A statistical p-value ≤ 0.01 is considered to be significant.

RESULTS

Comparison of Diabetes profile between study groups
In a comparison of Diabetes profile among the different study groups the mean levels of FBS, HbA1c, insulin, HOMA-IR were significantly higher ($P \leq 0.01$) in the patients groups than the controls group. as showen in figure 1.

Comparison of Lipid Profile between study groups
In a comparison of lipid profile among the different study groups the mean levels of triglycerides,LDL, and VLDL were significantly higher ($P \leq 0.01$) in the patients groups than the controls group.The mean level of vLDL was significantly higher in groups (DFU,IDFU and DM) than in the (controls) groups. has significant difference ($P \leq 0.01$) was found in the mean levels the patients groups of than the controls groupHDLbetween the study groups as showen in figure 2.

Comparison of Bone Health between study groups
When comparing the bone health profile of the different study groups, the mean phosphorus levels were significantly higher ($P \leq 0.01$) in the DFU, IDF groups compared to the control and DM groups. The mean calcium levels were significantly lower ($P \leq 0.01$) in the patient groups compared to the control group.as showen in figure 3.

Comparison Level of PCT ,vitamin D and OPN

When comparing the results of PCT and OPN concentration between the patient groups compared to the control group, a significant increase was observed ($P \leq 0.01$), while when comparing the vitamin D concentration between the patient groups compared to the control group, a significant decrease was observed ($P \leq 0.01$), as shown in figure 4.

PCT Levels :

In our study, the serum levels of procalcitonin (PCT) were measured in various patient groups and compared to a control group. The PCT levels in (DM), (DFU), and (IDFU) groups were found to be 0.054±0.066 ng/ml , 0.134±0.028 ng/ml , and 0.82±0.59 ng/ml , respectively, compared to 0.018 ± 0.015 ng/ml in the control group.

These findings are consistent with previous studies, although some variations in PCT levels were observed across different investigations. For instance: In studies by Korkmaz *et al.* ,(2018) slightly lower PCT levels were reported, with values of 0.6 ng/ml for infected diabetic foot ulcers (IDFU) and 0.15 ng/ml for non-infected diabetic foot ulcers (NDFU).

Similarly, Umapathy *et al.* ,(2018) reported comparable PCT levels of 0.50 ng/ml for IDFU and 0.06 ng/ml for NDFU. In contrast, higher PCT levels were observed in studies by Jafari *et al.* , (2014) with values of 1.2 ng/ml for IDFU and 0.33 ng/ml for NDFU, as well as in the work of El-Kafrawy *et al.* , (2019) which reported levels of 1.43 ng/ml for IDFU and 0.18 ng/ml for NDFU.

Vitamin D Levels :

Vitamin D levels differed significantly among the 4 groups of participants . Healthy individuals had higher vitamin D levels when compared with patients with The Vitamin D levels in (DM), (DFU), and (IDFU) groups were found to be 17.93±4.48 ng/ml, 15.71±4.76 ng/ml , and 13.30±4.42 ng/ml , respectively, compared to 39.08±10.64 ng/ml in the control group.This study is consistent with previous studies in which diabetic foot ulcer patients suffer from vitamin D deficiency.. In a study by Tsitsou *et al.*, (2023) , Vitamin D levels were reported as 19.8 ng/ml for DM patients and 17.9 ng/ml for diabetic foot ulcer (DFU) patients. Similarly, Tang *et al.* (2023) reported Vitamin D levels of 15.7 ng/ml for DM patients and 10.3 ng/ml for DFU patients.

OPN Levels:

In our study, the serum levels of Osteopontin (OPN) were measured in various patient groups and compared to a control group. The OPN levels in (DM), (DFU), and (IDFU) groups were found to be 19.44±6.94 ng/ml , 26.99±9.41 ng/ml , and 46.72±13.66 ng/ml , respectively, compared to 12.76±4.20 ng/ml in the control group.

These findings are consistent with previous studies, although some variations in OPN levels were observed across different investigations. For instance: In studies by AlKenany et al. ,(2024) OPN levels were found to be higher in diabetics compared to healthy individuals. In Similarly in the study of Al-Rawaf et al. ,(2021) was the OPN levels higher in DM patients compared with healthy.

The ROC Analysis of PCT , OPN and Vitamin D Parameters

The results of the ROC analysis indicate that PCT is effective in differentiating and predicting DFU patients from healthy individuals, with an area under the curve (AUC) of 94. The sensitivity and specificity values were 96% and 91%, respectively. Additionally, the P-value for the prior probability was found to be 0.001, as illustrated in Figure 5.

The results of the ROC analysis indicate that OPN is effective in differentiating and predicting DFU patients from healthy individuals, with an area under the curve (AUC) of 95. The sensitivity and specificity values were 92% and 84%, respectively. Additionally, the P-value for the prior probability was found to be 0.001, as illustrated in Figure 5.

The results of the ROC analysis indicate that vitamin D is effective in differentiating and predicting DFU patients from healthy individuals, with an area under the curve (AUC) of 81. The sensitivity and

specificity values were 64% and 88%, respectively. Additionally, the P-value for the prior probability was found to be 0.001, as illustrated in Figure 6.

DISCUSSION

Serum PCT concentration in healthy individuals is typically <0.1 μg/L. In the presence of bacterial infection, PCT increases, and the degree of rise correlates with the severity of the infection (Abbas and El-Yassin ., 2022).Jeandrot *et al.*, (2008) reported that PCT might be used to distinguish mildly infected from non-infected foot ulcers in diabetics.*Efat et al* (2018) claimed that PCT was the best biomarker for the diagnosis of IDFU, with a sensitivity of 23.3% and specificity of 100%.Mutluoğlu *et al* (2011) mention The serum level of PCT increases rapidly in response to severe bacterial infections, while remaining relatively low in cases of viral infections and non-specific inflammatory conditions. This specific response of PCT to bacterial infections has led to the suggestion that it could be used as a marker to differentiate between bacterial and viral infections, as well as non-infectious inflammatory responses. Research has demonstrated that PCT is more effective than other infection markers for diagnosing both systemic and localized bacterial infections, including in sepsis cases. Uzun *et al.* (2007) proposed that measuring PCT levels could serve as a significant diagnostic marker for diabetic foot infections. Vitamin D levels of the study groups . Vitamin D levels differed significantly among the 4 groups of participants ($P < 0.05$). Healthy individuals had higher vitamin D levels when compared with patients with DM , DFU and IDFU .Lin *et al.*, (2023) mention the Individuals with diabetic foot ulcers exhibited significantly lower levels of vitamin D, as well as a greater prevalence of vitamin D deficiency and severe deficiency when compared to both non-ulcerated diabetic individuals and a control group.Vitamin D has a positive impact on the healing process of diabetic foot ulcers by enhancing insulin resistance, reducing inflammation, and combating oxidative stress, which helps eliminate bacteria present in the wounds. Additionally, vitamin D and its active metabolite, 1,25-(OH)2 vitamin D3, are involved in the growth and differentiation of keratinocyte cells and fibroblasts, particularly by modulating growth factors and cytokines (Badralany and Manikam, 2023)25-hydroxyvitamin D plays a significant role in enhancing insulin sensitivity and influencing secretory transcription factors due to the presence of vitamin D receptors on pancreatic beta cells, adipocytes, and peripheral skeletal muscle cells. A deficiency in 25(OH)D is thought to play a major role in the development of diabetic foot ulcers (DFU), leading to inefficient removal of excess glucose from the bloodstream (Priyanto *et al.*, 2023).Liu et al (2024) indicates a possible connection between low vitamin D levels and diabetic foot ulcers (DFU), supported by several studies. Furthermore, a strong deficiency in vitamin D appears to heighten the risk of developing DFUs in diabetes patients (Liu *et al.*, 2024). Diabetic foot ulcers (DFU) and infections may be associated with vitamin D levels. that low levels of circulating 25(OH)D can lead to elevated inflammatory cytokines in patients with DFU, hindering the healing process. Supplementation with vitamin D may help lower these inflammatory markers and can be considered a viable approach for managing infections and promoting faster healing of DFU. Additionally, a severe deficiency in vitamin D may contribute to the risk of diabetic foot infections, and providing vitamin D supplements could enhance clinical outcomes. Overall, vitamin D supplementation shows promise for speeding up the healing of DFU (Macido *et al.*, 2018). Serum vitamin D was higher in patients with chronic diseases than that in patients without chronic diseases history. (Khalil *et al.*, 2022). Osteopontin is involved in the development of inflammatory diseases. OPN acts as a potent chemoattractant, promoting macrophage migration and stimulating interleukin-12 (IL-12) production, while inhibiting apoptosis and interleukin-10 (IL-10) production (Martín-Márquez *et al.,* 2023).OPN is a key regulator of adipose tissue inflammation, insulin resistance, and diabetes. Osteopontin is a key mediator in promoting adipose tissue-associated inflammation and negatively impacting the body's response to insulin. OPN deficiency has been shown to reduce adipose tissue inflammation and increase insulin sensitivity (Sinambela *et al.,* 2020).A study conducted by Pramodyanti et al. (2021) examined the relationship of osteopontin to bone. OPN is essential and plays an important role in bone metabolism, participating in the regulation of bone remodeling and demineralization processes. It is significantly involved in bone formation and contributes to the osteoclasts for the interstitial matrix of bone through

its interaction with surface αvβ3 integrin and its binding to CD44 receptors. OPN's effects on CD44-mediated osteoclast dysfunction are linked to the CD44.

CONCLUSION

Monitoring PCT , OPN and vitamin D3 levels may help identify and manage diabetic foot complications early, potentially reducing the likelihood of serious consequences such as amputation. Early detection and timely interventions based on PCT , OPN and vitamin D3 testing may be effective strategies for improving clinical outcomes for patients with diabetes. Continued research is needed to refine these methods and integrate them into standard clinical practice to provide better patient care.

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IDFU **N=25** **Mean ±SD**	DFU **N=25** **Mean ±SD**	**DM** **N=25** **Mean ±SD**	**Control** **N=25** **Mean ±SD**	**Medan + SD**
224.14±56.50a	218.44±72.18a	187.10±89.94b	86.28±5.53c	**FBS (mg/dl)**
10.12±2.64 a	9.342±2.31 a	7.542±1.49 b	4.5063±0.52c	**HBA1C %**
15.96±3.02a	14.06±4.64 b	b13.07±3.07b	1.24±1.24c	**Insulin (µU/mL)**
8.84±2.96 a	7.68±3.77a	6.01±3.24b	0.77±0.26 c	**HOMA-IR**

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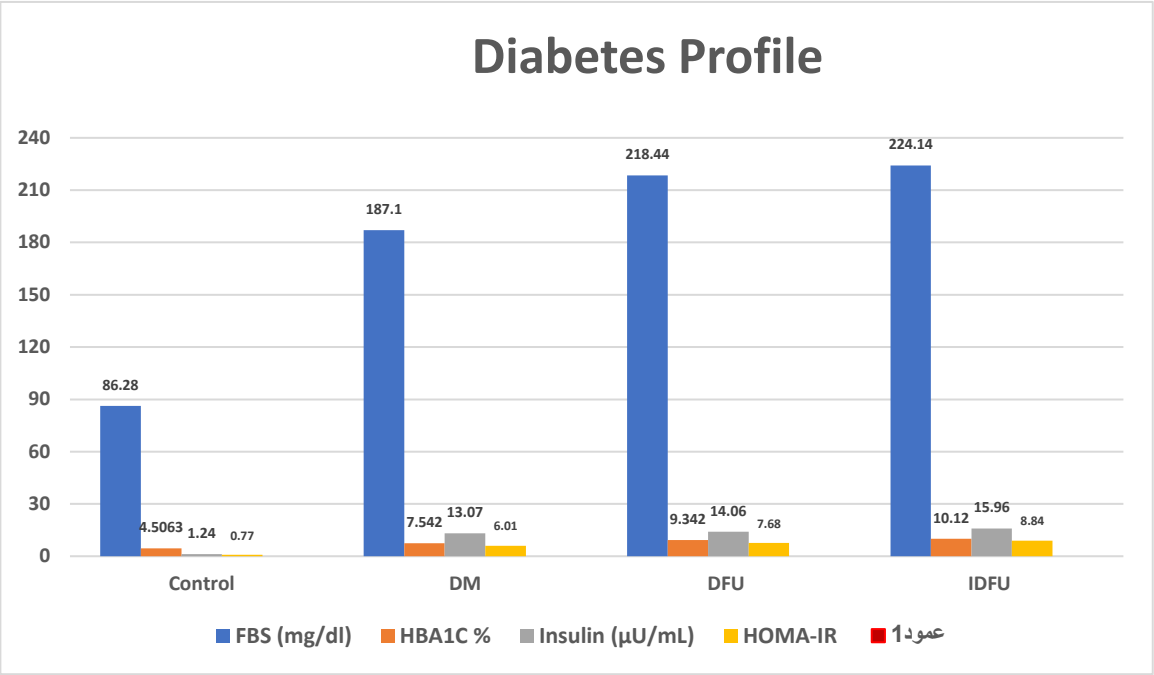

Figure (1) Diabetes profile between study groups

IDFU N=25 Mean ±SD	DFU N=25 Mean ±SD	DM N=25 Mean ±SD	Control N=25 Mean ±SD	Medan + SD
228.64±98.71a	222.76±89.87a	211.58±43.36a	92.49±5.66 b	(mg/dl) Triglyceride
240.20±47.29a	228.60±53.13a	217.26±46.79a	136.51±16.14b	(mg/dl) Cholesterol
25.88±4.31c	27.44±4.23c	32.46±6.37b	57.16±15.44a	HDL(mg/dl)
168.59±43.38a	156.61±41.62ab	142.48±48.41b	60.84±18.45c	LDL(mg/dl)
45.72±19.74a	44.55±17.97a	42.31± 8.67 a	18.50±1.12 b	VLDL(mg/dl)

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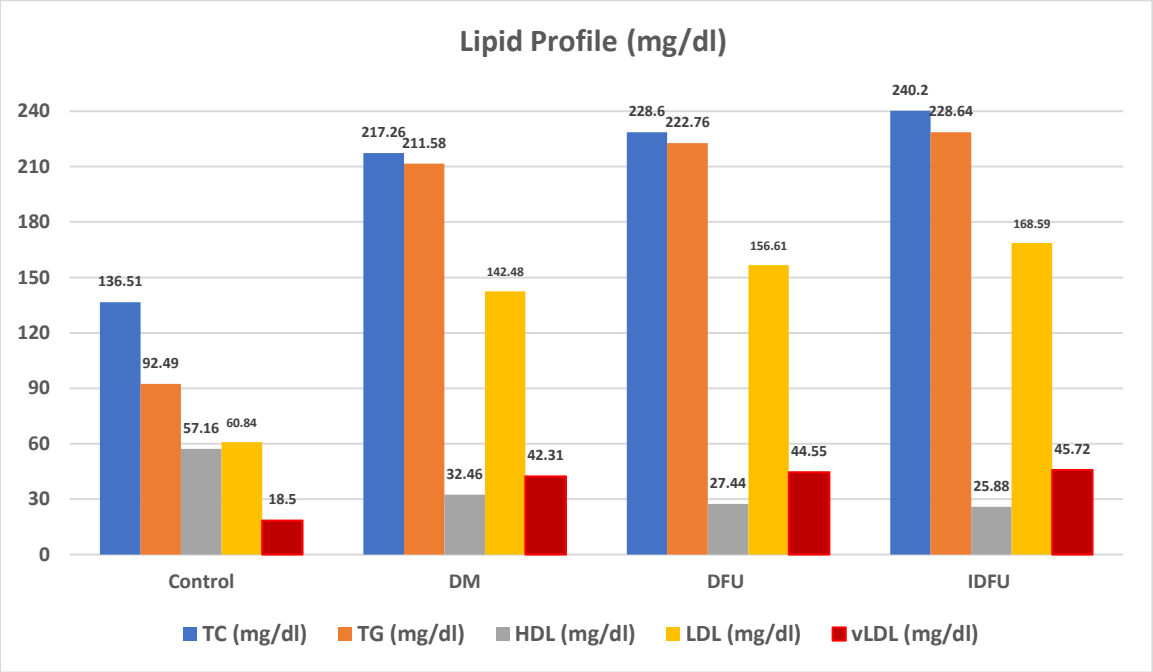

Figure (2) Lipid Profile study groups

IDFU N=25 Mean ±SD	DFU N=25 Mean ±SD	DM N=25 Mean ±SD	Control N=25 Mean ±SD	Medan + SD
5.26±0.79 a	5.51±0.61 a	5.36±0.59 b	2.93±0.58 b	Phosphor(mg/dl)
8.10±0.94b	8.16±0.09 b	8.21±0.21b	9.46±0.63a	Calcium(mg/dl)

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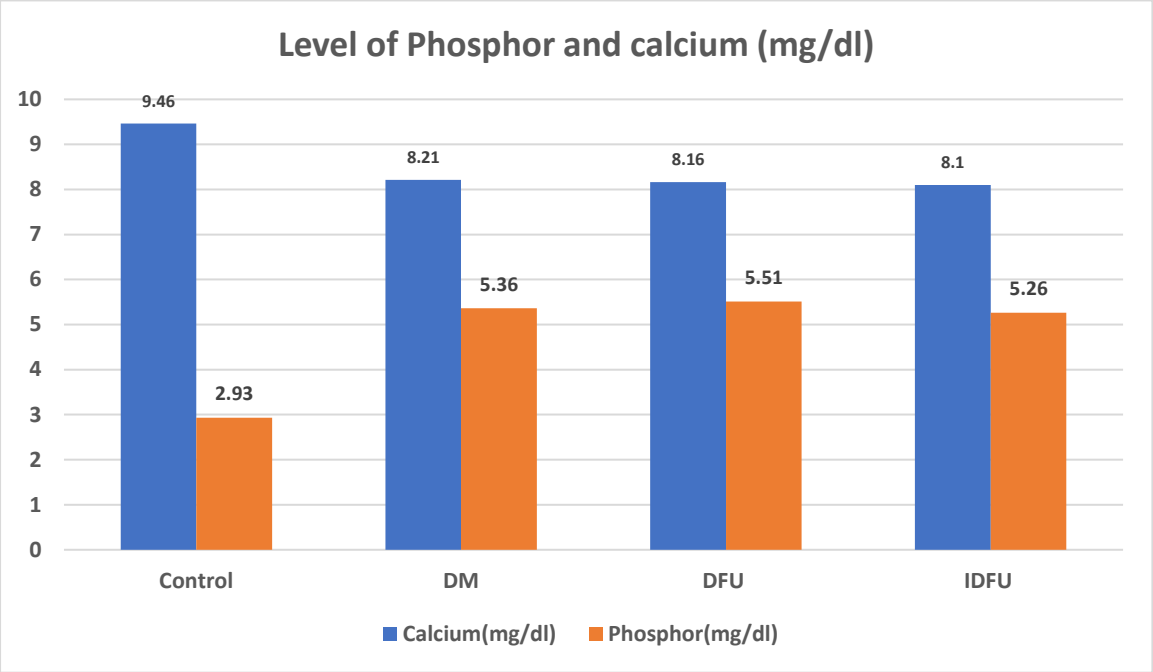

Figure (3) Phosphor and calcium study groups

IDFU N=25 Mean ±SD	DFU N=25 Mean ±SD	DM N=25 Mean ±SD	Control N=25 Mean ±SD	Medan + SD
46.72±13.66 a	26.99±9.41 b	19.44±6.94 c	12.76±4.20d	**OPN (ng/ml)**
13.30±4.42 c	15.71±4.76bc	17.93±4.48b	39.08±10.64a	**VITD (ng/ml)**
0.82±0.59 a	0.134±0.028b	0.054±0.066 c	0.018±0.015d	**PCT (ng/ml)**

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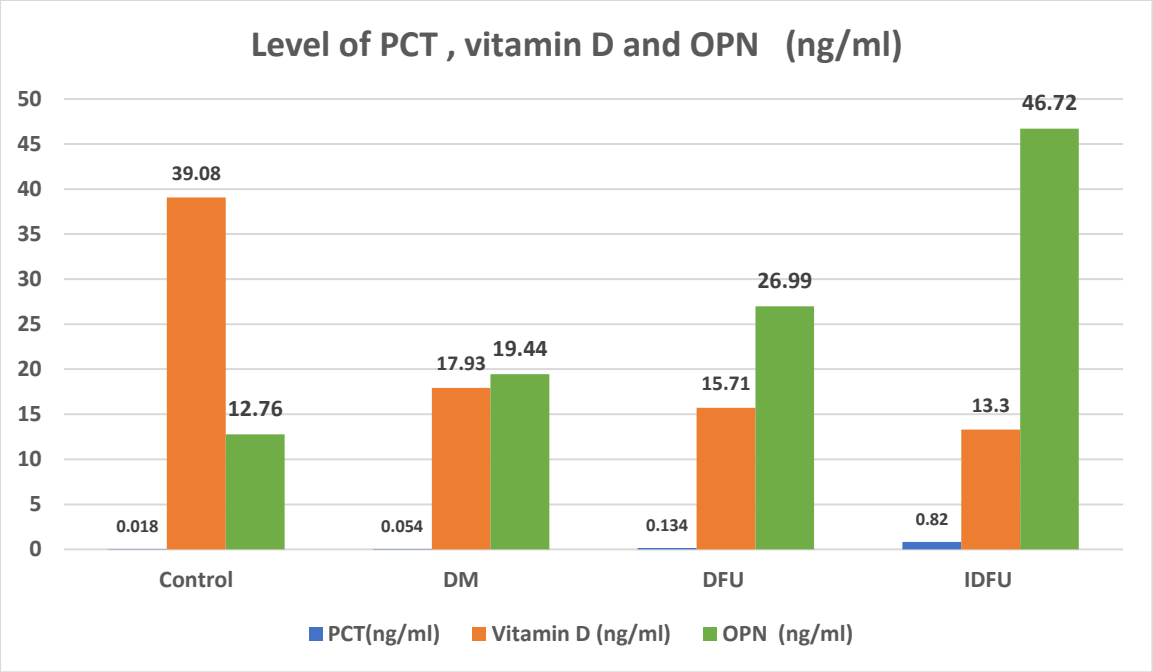

Figure (4) Level of PCT , vitamin D and OPN study groups

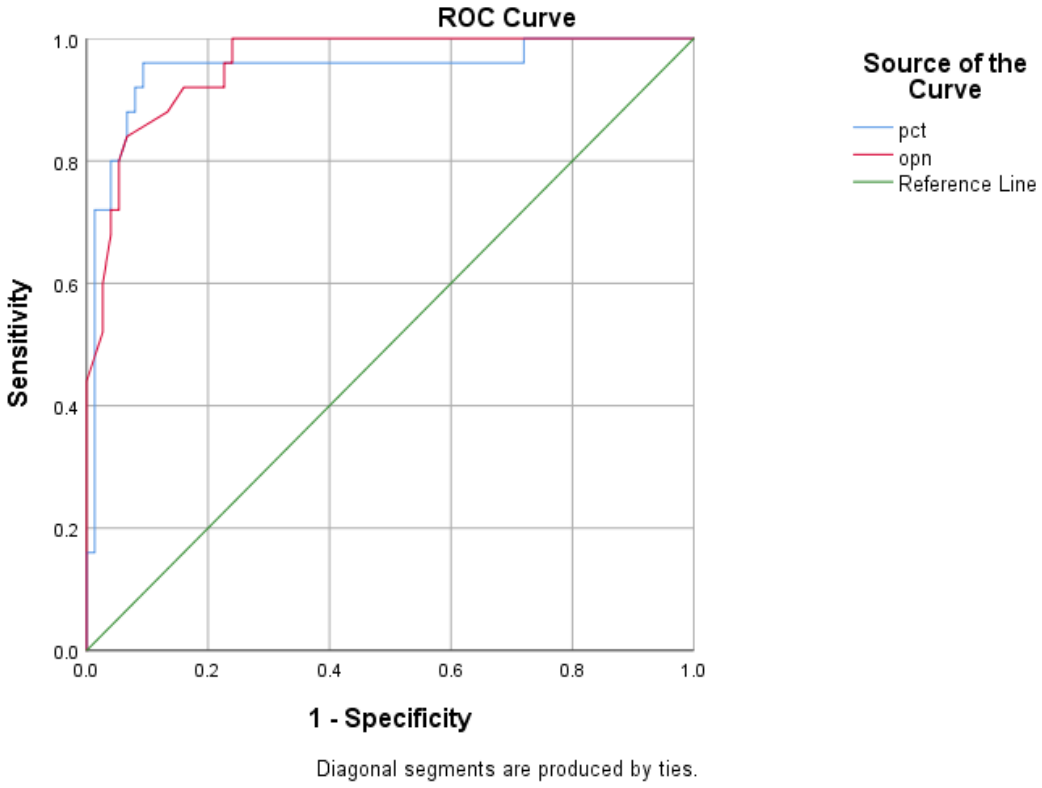

Figure (5) The ROC Analysis of PCT and OPN Parameters

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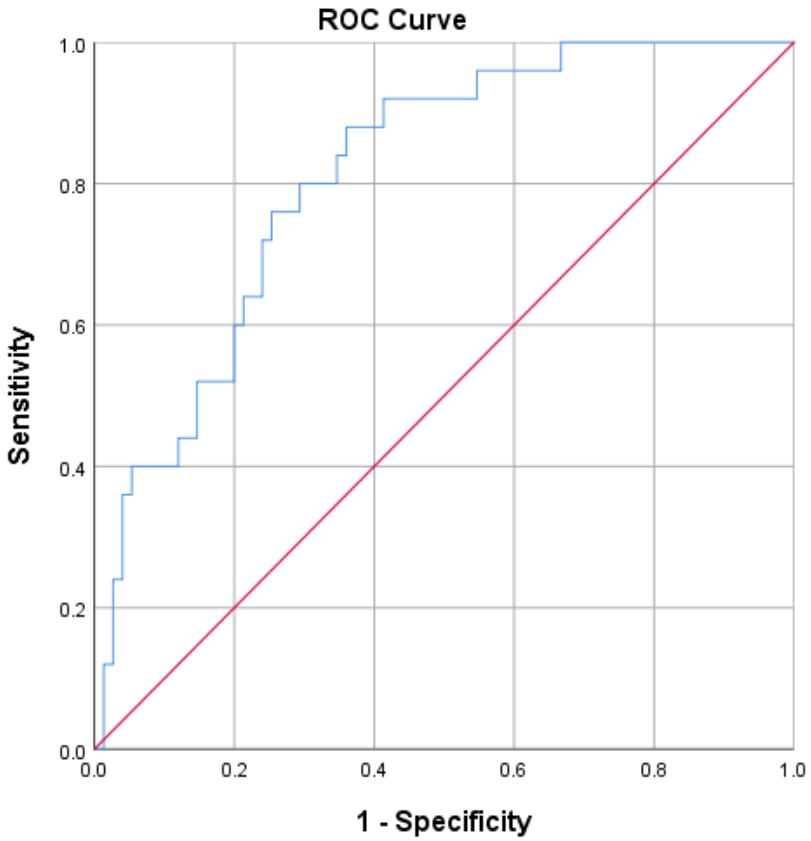

Figure (6) The ROC Analysis of vitamin D Parameter