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The Relationship Between Osteopontin Levels, Parathyroid Hormone, and Alkaline Phosphatase in Chronic Kidney Disease Patients: A Marker for Mineral and Bone Diseases

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ABSTRACT

Background: The 5th stage of renal failure is known as ESRD, which requires dialysis or transplantation of the kidneys. CKD leads to metabolism impairment of P, Ca2+, PTH, and vitamin D. CKD-MBD is described as CKD that has resulted biochemical laboratory irregularities, severe disease of the bones, and/or calcification of the vascular system. OPN is a calcium-binding glycol-phosphoprotein discovered in bones. OPN is associated with eGFR, iPTH, AP, and ionized calcium. **Aim:** To assess the OPN levels in CKD stages (3, 4, and 5) ND and stage 5 on (HD), as well as their relationship with PTH and AP, and to determine if OPN may be used as a marker for CKD/MBD. **Material and methods**: The cross-sectional investigation comprised 80 patients with CKD at nephrology and hemodialysis units at Tanta University Hospitals (six months). They were separated into two groups. 1) 40 individuals with CKD stage 5-HD. 2) 40 patients with CKD stages 3, 4, and 5-ND. All participants underwent a complete history, clinical examination, and laboratory investigations, including kidney function tests (urea, creatinine, GFR, eGFR, serum ionized calcium level, serum phosphorus level, serum alkaline phosphatase, serum iPTH level, serum osteopontin level), and radiological investigations (abdominal ultrasound). **Results:** In terms of calcium supplementation and vitamin D, the hemodialysis group performed significantly better than the CKD group. The hemodialysis group had substantially greater levels of osteopontin and PTH compared to the CKD group ($p < 0.001$). While alkaline phosphatase levels were considerably lower in the hemodialysis group. In both groups, osteopontin was positively linked with alkaline phosphatase ($p=0.003$) and PTH ($p <0.001$). Osteopontin had good sensitivity and specificity in predicting CKD-MBD in the hemodialysis group (99.9%, 99.9%) and ($p <0.001$), and acceptable in the CKD group (90.9%, 87%) ($p < 0.001$). **Conclusion:** OPN correlated significantly with CKD-MBD markers. OPNO levels are a useful indicator for predicting mineral bone damage in CKD patients.

Keywords: Osteopontin, CKD-MBD, Ca2+, PTH, vitamin D

1. Introduction

(CKD) is known as kidney structural or function anomalies that have been present for at least three months and have serious health consequences (Levin and Stevens, 2014). ESRD is grade 5 CKD when eGFR is less than 15 ml/min/1.73m2, necessitating renal replacement treatment (dialysis or kidney transplant) (Levin and Stevens, 2014; Hsu *et al.,* 2008). Anemia, dyslipidemia, malnutrition, cardiovascular problems, and chronic kidney disease-mineral bone disease (CKD-MBD) are all consequences of deteriorating kidney function, and they are linked with increased morbidity and mortality, particularly in ESRD patients (Thomas *et al.,* 2017).

The defect in bone and mineral metabolism is known as CKD-MBD, which includes one or more of the following (Improper metabolism of phosphorus, calcium, parathyroid hormone (PTH), or

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Vitamin D; 2. Irregular bone turnover, mineralization, volume, linear growth, or strength, and 3. Vascular or soft-tissue calcification). The diagnosis of CKD MBD with bone biopsy is intrusive; also, histomorphometry facilities are not widely available, particularly in underdeveloped countries. Serum calcium, phosphorus, PTH, and alkaline phosphatase levels are commonly used to screen for CKD-MBD (Ketteler *et al.,* 2017).

Osteopontin (OPN) which was expressed in the thick part of the ascending limb of the loop of Henle (Cer and Gezmen-Karadag, 2018) is a glycol-phosphoprotein that can be found also in Inflammatory, epithelial, and endothelial cells. OPN can be presented in bone smooth muscle, neurons, and fetal renal tissue. OPN functions include increasing macrophage and T-cell counts, stimulating inflammation, wound healing, cancer development and progression, diabetes, and maybe controlling nephrolithiasis and nephrogenesis (Kaleta, 2019).

OPN affects both calcifications in the arteries and the mineralization of bones. Local increases in OPN in vessel walls have been related to atherosclerotic plaque formation, arterial inflammation, and smooth muscle mineralization (Cer and Gezmen-Karadag, 2018; Scatena *et al.,* 2007; Abdalrhim *et al.,* 2016).

A selection of biomarkers has been investigated in CKD-MBD, however, there is a strong need for further characterization of new indicators, particularly in the setting of CKD5-HD. Serum OPN monitoring may address the need for better CKD-MBD diagnosis and treatment (Alderson *et al.,* 2013; Tan and Cai, 2017; Ortiz *et al.,* 2011).

The study purpose was to assess the blood levels of OPN in CKD stage (3, 4, and 5)-ND and stage 5-HD patients, as well as their relationship with Parathyroid hormone and Alkaline phosphatase, i. Ca, and their potential as a marker for CKD-MBD.

2. Patients & Methods

Study Design: A cross-sectional research study.

Study population: This prospective study included 80 CKD patients recruited from different nephrology and hemodialysis facilities at Tan University Hospitals.

The study population was divided into 2 groups: **Group A**: 40 patients of CKD stage 5-HD and **Group B:** 40 patients of CKD stage (3, 4 & 5)-NH.

Inclusion criteria: CKD fifth-stage subjects undergoing hemodialysis maintenance. And CKD stage (3, 4 &5) not on dialysis patients.

Exclusion criteria: CKD patients with tertiary hyperparathyroidism. CKD patients with a history of parathyroidectomy. CKD stage (1,2) patients.

Each of the subjects was tested to 1. Complete history taking: (age, gender, BMI, comorbidities, prescriptions, and supplements) 2. Complete clinical examination. 3. Laboratory investigations (kidney function tests (urea, creatinine, and eGFR), Serum ionized ca level, Serum phosphorous level, Serum alkaline phosphatase, Serum iPTH level. 4.Osteopontin level. 5. Radiological investigations: (Abdominal ultrasound).

3. Results

Table (1) demonstrated that the mean osteopontin, phosphorus and PTH were significantly higher in hemodialysis group (156.73 ± 12.890 ng/ml, 5.05 ±1.027 mg/ dl and 348.90 ± 66.897 pg/ml respectively) than inthe CKD group (21.00 ± 2.385 ng/ml, 3.90 ± 0.868 mg/ dl and 160.61 ± 45.094 pg/ ml respectively). While the mean AP and i.Ca were significantly lower in the hemodialysis group (7.70 ± 1.275 U/L, 1.01 ± 0.120 mmol/L respectively) than in the CKD group (57.63 ± 3.083 U/L, 1.12 ± 0.119 mmol/L respectively)

Table 1: CKD-MPD markers of the studied groups:

	Hemodialysis group (n= 40)	CKD group (n= 40)	95% CI	P
Osteopontin (ng/mL)	156.73 ± 12.890	21.00 ± 2.385	131.6, 139.9	**< 0.001**
Alkaline phosphatase (U/L)	7.70 ± 1.275	57.63 ± 3.083	-51.0, -48.9	**< 0.001**
PTH (pg/ mL)	348.90 ± 66.897	160.61 ± 45.094	162.9, 213.7	**< 0.001**
Ionized calcium (mg/dL)	1.01 ± 0.120	1.12 ± 0.119	-0.2, - 0.1	**< 0.001**
Phosphorus (mg/dL)	5.05 ± 1.027	3.90 ± 0.868	0.7, 1.6	**< 0.001**

The data presented in Table 2 and Figures 1- 4 demonstrated that in the hemodialysis group (group 1) osteopontin was strongly positively linked with eGFR (r= 0.411, p=0.008), alkaline phosphatase (r= 0.456, p= 0.003), and PTH (r= 0.529, p = 0.001). While it had a significant negative correlation with ionized calcium (r = -0.367, p = 0.020). In the CKD group (group 2), osteopontin (r= 0.575, p<0.001) was strongly positively linked with alkaline phosphatase (r= 0.791, p<0.001) and PTH (r= 0.776, p<0.001) levels. It had a significant negative correlation with ionized calcium (r = -0.418, p = 0.007).

Table 2: Correlation between osteopontin and other studied variables

Osteopontin (ng/mL)	**Hemodialysis group (n= 40)**		**CKD group (n= 40)**	
	R	**P**	**r**	**P**
Stage	-	-	0.575	**< 0.001**
eGFR	0.411	**0.008**	0.183	0.257
Ionized calcium	-0.367	**0.020**	-0.418	**0.007**
Phosphorus	0.022	0.891	-0.156	0.337
Alkaline phosphatase	0.456	**0.003**	0.791	**< 0.001**
PTH	0.529	**< 0.001**	0.776	**< 0.001**
P is significant when < 0.05.				

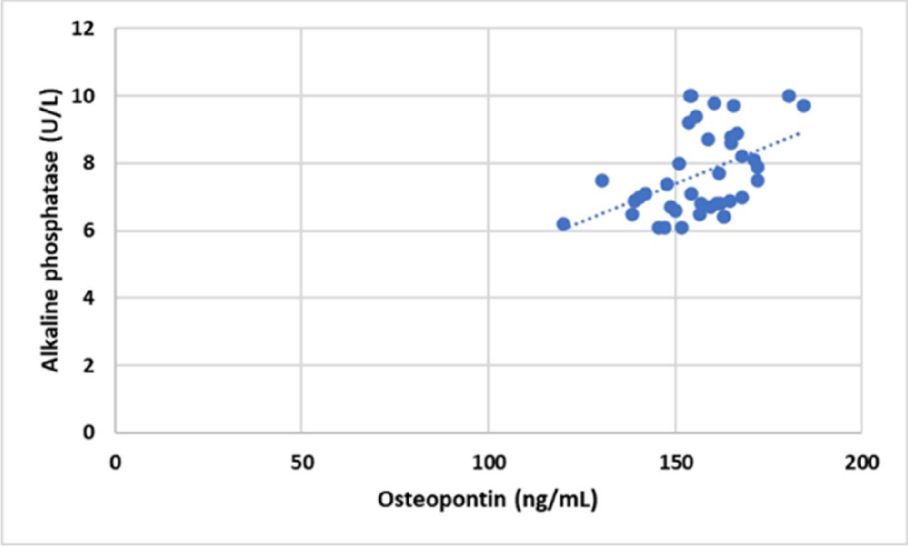

Fig. 1: Correlation between osteopontin and Alkaline phosphatase in Hemodialysis group

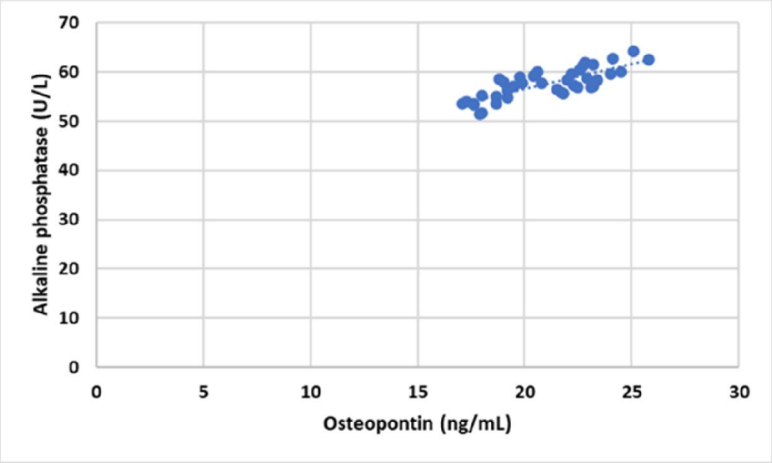

Fig. 2: Correlation between osteopontin and Alkaline phosphatase in CKD group

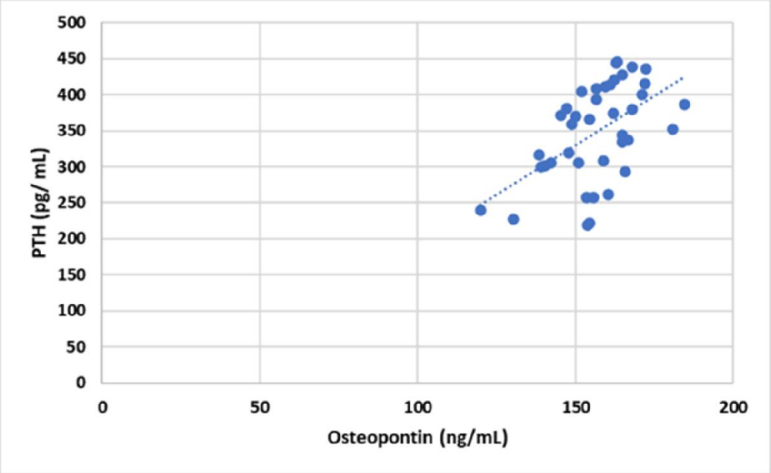

Fig. 3: Correlation between osteopontin and PTH in Hemodialysis group

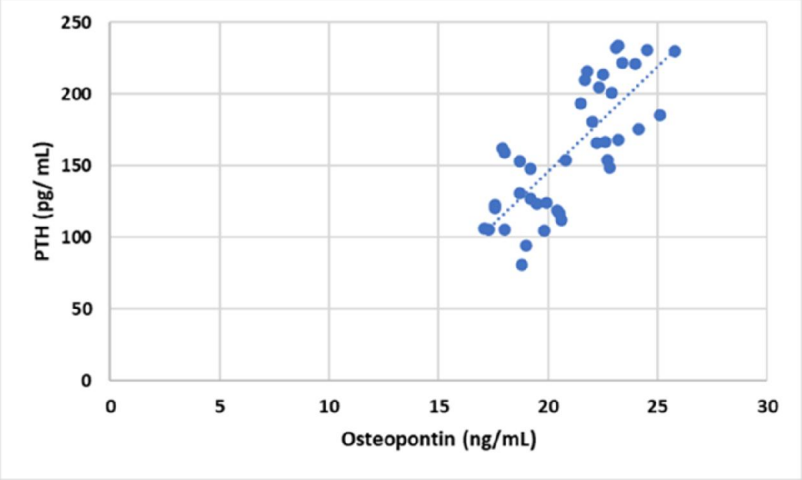

Fig. 4: Correlation between osteopontin and PTH in CKD group

Table 3 and figures 5 and 6 showed that osteopontin is accurate with a significant area under curve of 0.999 for diagnosis of CKD-MBD in hemodialysis. At osteopontin 72.85 maximum

sensitivity is 99.9%, specificity is 99.9%, PPV is 99.9%, NPV is 99.9% with accuracy 100%. Osteopontin is acceptable with a significant area under curve of 0.804 for prediction of CKD-MBD in stage V. At osteopontin >19.9, maximum sensitivity is 88.8 %, specificity is 963.64 %, PPV is 66.7 %, NPV is 87.5 % with accuracy 75.0 %.

Table 3: Diagnostic profile of osteopontin in diagnosis of presence of hemodialysis

Osteopontin (ng/mL)	Hemodialysis	Non- Hemodialysis (Stage V)
AUC	0.999	0.804
P	**< 0.001**	0.001*
Cut-off point	72.85	>19.9
Sensitivity	99.9%	88.89
Specificity	99.9%	63.64
PPV	99.9%	66.7
NPV	99.9%	87.5
Accuracy	100.0%	75.0

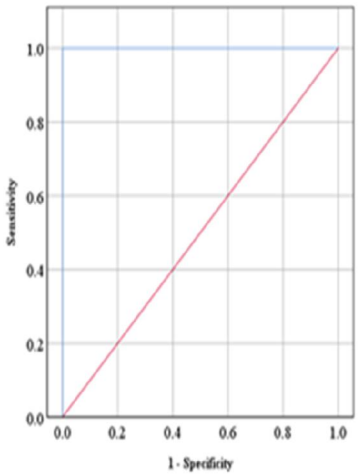

Fig. 5: ROC curve for Diagnostic profile of Osteopontin in diagnosis of presence of Hemodialysis group

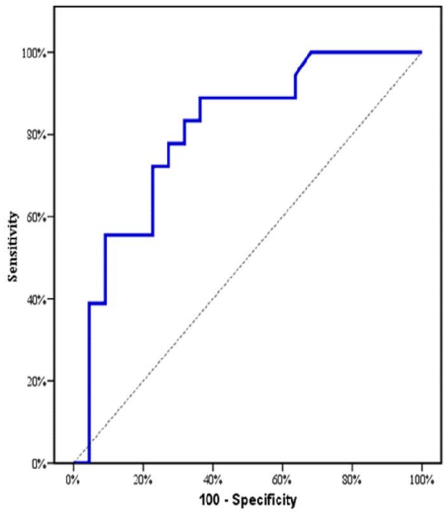

Fig. 6: ROC curve for serum osteopontin's performance in predicting CKD-MBD in the CKD group at stage V.

4. Discussion

Our findings showed that the mean ionized calcium was substantially lower in the hemodialysis group compared to the CKD group, whereas the mean phosphorus was significantly greater. This is consistent with the findings of Ganesha Pandian (2018), who found a statistically significant rise in serum phosphorus levels in CKD patients compared to controls.

Nawar *et al.* (2022) showed a statistically significant change between the studied groups regarding total calcium (lower in the CKD cases group), phosphorus, and PTH (both greater in the case group).

According to the current study, the mean alkaline phosphatase level was considerably greater in the CKD group compared to the hemodialysis group. The Ganesha Pandian (2018) study included 50 patients in varying stages of CKD and 50 controls. To correlate serum intact PTH, phosphorus, and alkaline phosphatase levels in different phases of CKD and compare them to the control group. To determine the function of intact parathyroid hormone in the early detection of mineral abnormalities in CKD patients. It found that alkaline phosphatase levels were higher in cases than in controls, but this was only significant at stage 5.

Natikar *et al.* (2020) found that there was an increase in alkaline phosphatase levels in the cases group (50 CKD patients) compared to the control group (50 seemingly healthy persons), but it was not statistically significant. According to the study's findings, the mean osteopontin level rises dramatically as CKD stages advance. These findings are like Barreto *et al.* (2011) research in CKD, which showed that OPN levels increased from the early stages of CKD onward. The beneficial relationship between OPN and clinical outcomes was affected by the patients' inflammatory condition.

Also, following Al-Obaidy and Al-Zubaidi (2020), plasma OPN levels were related to the severity of renal function impairment. Similarly, Druck *et al.* (2019) found a substantial rise in plasma OPN levels in individuals with CKD5-HD. The results of Nawar *et al.* (2022) revealed that the case group had considerably increased osteopontin levels.

Regarding our findings, the mean PTH levels showed a statistically significant increase with the CKD stage. According to Ganesha Pandian (2018), CKD patients have significantly higher PTH levels than controls. They observed that PTH levels are slightly raised in stage III CKD, moderately elevated in stage IV CKD, and dramatically elevated in stage V CKD.

Our findings revealed that osteopontin was considerably favorably connected with eGFR, alkaline phosphatase, and PTH in both the hemodialysis and CKD groups, but significantly negatively correlated with ionized calcium. Similarly, Nawar *et al.* (2022) found a favorable relationship between blood OPN levels and alkaline phosphatase, PTH, and phosphorus serums. In terms of serum calcium, there was no significant association between OPN and calcium.

Druck *et al.* (2019) discovered a favorable association between alkaline phosphatase and PTH serums, however, there was no link between OPN and serum phosphorus.

In CKD patients (K/DOQI stages 1–5), Lorenzen *et al.* (2010) study showed that OPN plasma concentrations correlate negatively with GFR but positively with other renal function markers such as serum creatinine.

Our findings indicate that serum osteopontin performs well in predicting CKD-MBD in hemodialysis, with a substantial area under the curve of 0.999. The optimum serum osteopontin cutoff for predicting CKD-MBD in hemodialysis is 72.85; maximal sensitivity is 99.9%, specificity is 99.9%, PPV is 99.9%, NPV is 99.9%, and accuracy is 100%.

Osteopontin is an acceptable predictor of CKD-MBD in the CKD stage III group, with a substantial area under the curve of 0.862. At osteopontin ≤20.8, the maximal sensitivity is 90.91%, specificity is 85.51%, PPV is 50.0%, NPV is 96.8%, and accuracy is 87.0%. Osteopontin is an acceptable predictor of CKD-MBD in the CKD stage V group, with a substantial area under the curve of 0.804. At osteopontin levels over 19.9, the maximal sensitivity is 88.8%, specificity is 963.64%, PPV is 66.7%, NPV is 87.5%, and accuracy is 75.0%.

In the study by Nawar *et al.* (2022), the most accurate cutoff for osteopontin level in expecting CKD was ≥31.1, with an AUC of 0.995, a sensitivity level of 98.8%, specificity of 95%, PPV of 95.2%, NPV of 98.7%, and accuracy of 96.9% ($p<0.05$).

There is a dearth of research on OPN in CKD and its association to CKD-MBD bone indicators; nonetheless, the blood OPN test provides an excellent biomarker for early detection of CKD.

Our study has a few drawbacks, such as the sample size is restricted, and it was collected many times over the day. Circadian rhythm and diet might have influenced the observed protein and mineral levels. Each patient's time since starting dialysis vary, which might have altered levels of various biomarkers. Patients with CKD5-HD had a significant number of comorbidities, such as diabetes, hypertension, and coronary/peripheral artery disease, which may have affected Ca2, P, OPN, and iPTH values. Serum bicarbonate and bone-specific AP have not been studied in CKD-MBD due to the limited strength of KDIGO's recommendations and the expensive cost of additional laboratory testing.

5. Conclusion

This study found a substantial increase in OPN among the tested groups (different CKD stages), with hemodialysis patients having the highest levels. Furthermore, OPN showed a substantial connection with CKD-MBD markers. These data imply that OPN can play a critical role in Ion balance, calcification of vessels, and turnover of bone. The study suggested that osteopontin might be a useful marker for early prediction of MBD activity in CKD patients.

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