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## **Assessment of osteoprotegerin as bone marker in chronic kidney disease patients**

**Baraa Khalid Khalef**

M.Sc., Biochemistry Department, College of Medicine, University of Babylon, Hillah, Iraq

**Thana Mohammed Joda**

Assistant Prof., Biochemistry Department, College of Medicine, University of Babylon, Hillah, Iraq

**Ali Jasim Al-Sultani**

Assistant Prof., Biochemistry Department, College of Medicine, University of Babylon, Hillah, Iraq

**Abstract**---Chronic kidney disease is a chronic impairment in the structure or function of the kidney. (eg, glomerular filtration rate [GFR] <60 mL/min/1.73 m<sup>2</sup> or albuminuria ≥30 mg per 24 hours) for more than 3 months. Renal osteodystrophy is a change in bone morphology in CKD patients, and it is one marker of the skeletal component of the systemic condition of chronic kidney disease mineral bone disease (CKD-MBD) that can be quantified using histomorphometry on bone biopsies chronic kidney disease mineral bone disease (CKD-MBD) defines a complex syndrome of renal osteodystrophy, mineral disorders and cardiovascular disease in patients with chronic kidney disease. The study was a case –control design which conducted in Dialysis Unit in AL-Mahmoodia General Hospital and ALyarmook Teaching Hospital in Baghdad. This study was carried out in private laboratories between September 2021 to march 2022. In this investigation, the total subjects were 90, the patient group was consist of 45 Hemodialysis (HD) (CKD) ( 18 males and 27 females). This study was showed most age of CKD cases, was (41-65) years. The results referred to the increased levels, Osteoprotegerin (OPG), Parathyroid hormone (PTH), alkaline phosphatase (ALP) and phosphorus in CKD patients with highly significant differences ( $P \leq 0.01$ ) when compared with control group, while there were decrease in calcium and albumin in patient group ( $P \leq 0.01$ ). The bone metabolism biomarkers are increased in CKD patients who complicated to renal osteodystrophy (ROD) and chronic kidney disease mineral bone disease CKD-MBD.

**Keywords**---osteoprotegerin (OPG), metabolic bone disease, chronic kidney disease, renal osteodystrophy (ROD).

## **Introduction**

Chronic kidney disease is a clinical condition caused by a permanent alteration in kidney function and/or Structure. It is characterised by its irreversibility as well as its gradual and steady progression(1).Is defined as a chronic impairment in the structure or function of the kidney. (eg, glomerular filtration rate [GFR] <60 mL/min/1.73 m<sup>2</sup> or albuminuria ≥30 mg per 24 hours) for more than 3 months(2, 3). Renal osteodystrophy is a change in bone morphology in CKD patients, and it is one marker of the skeletal component of the systemic condition of chronic kidney disease mineral bone disease (CKD-MBD) that can be quantified using histomorphometry on bone biopsies (4). Chronic kidney disease mineral bone disease (CKD-MBD) defines a complex syndrome of renal osteodystrophy, mineral disorders and cardiovascular disease in patients with chronic kidney disease. (5) Characteristics of CKD-MBD Inappropriate parathyroid hormone (PTH), phosphorus, calcium, vitamin D metabolism, Defects in bone metabolism, mineralization, volume linear growth, or strength ,soft-tissue calcifications (vascular calcifications). The most prevalent consequences associated with CKD-MBD are uremic vascular calcification and osteoporosis (6, 7).

Osteoprotegerin (OPG) OPG is generally considered to be a secreted soluble receptor and is produced by many different tissues and cell types including osteoblasts.it has key roles in bone biology and the immune system(8). The role of OPG is used as a decoy receptor for RANKL and inhibitor of osteoclastogenesis. Osteoprotegerin (OPG) is a glycoprotein that belongs to the tumor necrosis factor receptor superfamily(9). Serum, plasma EDTA, citrate, and heparin samples can all be tested for OPG. Sandwich ELISA techniques for evaluating OPG are commercially available and use monoclonal capture and polyclonal detection antibodies. However, further evidence is needed to support the clinical utility of serum OPG as a biomarker for assessing bone disease activity (10).

In individuals with renal illness, OPG might be a biomarker. Circulating OPG levels are higher in CKD patients on predialysis, dialysis, and transplant, and they may indicate vascular calcification development and patient survival. Circulating OPG, on the other hand, is reduced in nephrotic syndrome. Despite the link between high OPG levels and illness, experimental functional data shows that OPG may be beneficial in renal disease and vascular damage in the context of uremia. Thus, tissue injury causes an increase in OPG, whereas OPG may protect against tissue harm(11). Osteoblasts mediate osteoclastogenesis by expressing the membrane-associated cytokine receptor activator of nuclear factor-kappa B ligand (RANKL). Osteoprotegerin (OPG) is a soluble RANKL decoy receptor that is primarily generated by osteoblasts and inhibits the RANKL-RANKL receptor interaction, hence preventing osteoclast development and osteoclastic bone resorption(12, 13).

## Materials and Method

The study was a case –control design which conducted in Dialysis Unit in AL-Mahmoodia General Hospital and ALyarmook Teaching Hospital in Baghdad. This study was carried out in private laboratories between September 2021to march 2022. In this investigation,the total subjects were 90, the patient group was Consist of 45 Hemodialysis (HD) (CKD) ( 18 males and 27 females). All patients were diagnosed by a specialist physician when they attended to heamodialysis Unit at alyarmouk Teaching Hospital and almahmmodia general hospital, control group consist of 45 healthy individuals (27 females and 18 males). The levels of alkaline phosphatase (ALP) activity,calcium ,albumin and phosphrouse in serum, were determined by spectrophotometric method. Serum OPG,parathyroid PTH level were estimated by sandwich ELISA technique

## Results

This study was showed most age of CKD cases, was (41-65) years.as seen in figure (1). The mean  $\pm$  SD of OPG levels for CKD patients and control ( $219.54 \pm 56.31$ ,  $4.88 \pm 0.61$  ng/mL) respectively and P-value 0.0001 as showed in table (1) & figure (2), and The mean  $\pm$  SD of ALP levels for CKD patients and control ( $381.71 \pm 46.62$ ,  $86.37 \pm 4.46$  U / L) respectively , P-value 0.0001 as showed in table (1) . But the mean  $\pm$  SD of PTH levels for CKD patients and control ( $858.03 \pm 42.62$ ,  $613.84 \pm 23.12$ ), P-value 0.0001 as showed in table (1) .while table (2) and figure (3) represents The mean  $\pm$  SD of calcium, phosphorus and albumin levels for CKD patients and control respectively ( $7.34 \pm 0.16$ ,  $8.98 \pm 0.08$ mg/dl,  $6.46 \pm 0.36$ ,  $2.68 \pm 0.03$  mg/dl,  $3.72 \pm 0.07$ ,  $4.47 \pm 0.05$ g/dl). Predictor of OPG CKD-MD patients form controls Groups Figure (4) shows the ROC curve between well CKD-MD patients and controls. The test revealed that the area under the curve (AUC) was 0.962 (standard error) 0.18, 95 % CI = 0.92 – 0.99, p=0.0003. The sensitivity and specificity of the test at the cut-off value of  $\geq 26.9$  ng/mL were 88.4% and 75.6%, respectively, indicating a fair discriminative value.

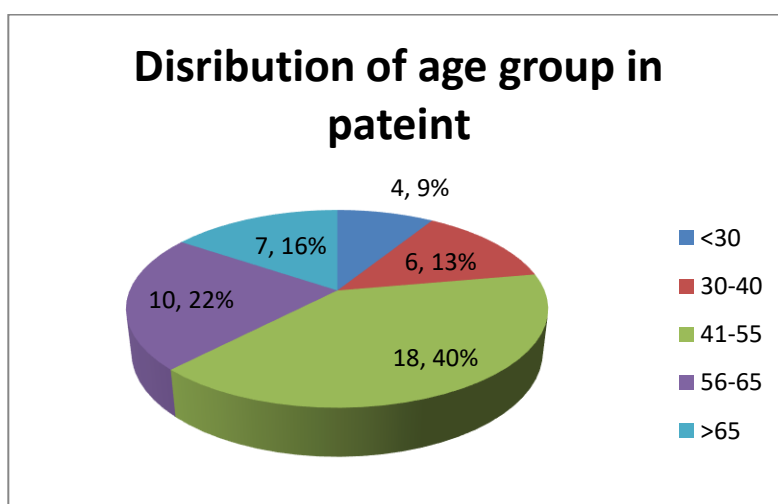


Figure 1. distribution of age groups in CKD patients

Table 1  
Comparison between patients and control in OPG, ALP, and PTH

Group	Mean $\pm$ SE		
	OPG (ng/mL)	ALP (U/l)	PTH (pg/ml)
Patients	219.54 $\pm$ 56.31	381.71 $\pm$ 46.62	858.03 $\pm$ 42.62
Control	4.88 $\pm$ 0.61	86.37 $\pm$ 4.46	613.84 $\pm$ 23.12
T-test	111.93 **	93.081 **	96.375 **
P-value	0.0003	0.0001	0.0001
** (P $\leq$ 0.01).			

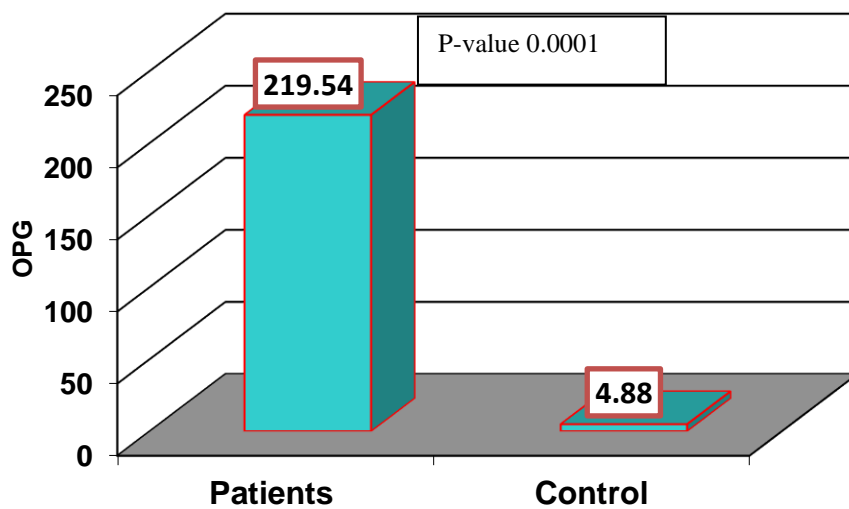


Figure 2. OPG levels in CKD patients & control

Table 2  
Comparison between patients and control in Ca, P and Albumin

Group	Mean $\pm$ SE		
	Ca (mg/ dl)	P (mg/dl)	Alb (g/dl)
Patients	7.34 $\pm$ 0.16	6.46 $\pm$ 0.36	3.72 $\pm$ 0.07
Control	8.98 $\pm$ 0.08	2.68 $\pm$ 0.03	4.47 $\pm$ 0.05
T-test	0.373 **	0.738 **	0.177 **
P-value	0.0001	0.0001	0.0001
** (P $\leq$ 0.01).			

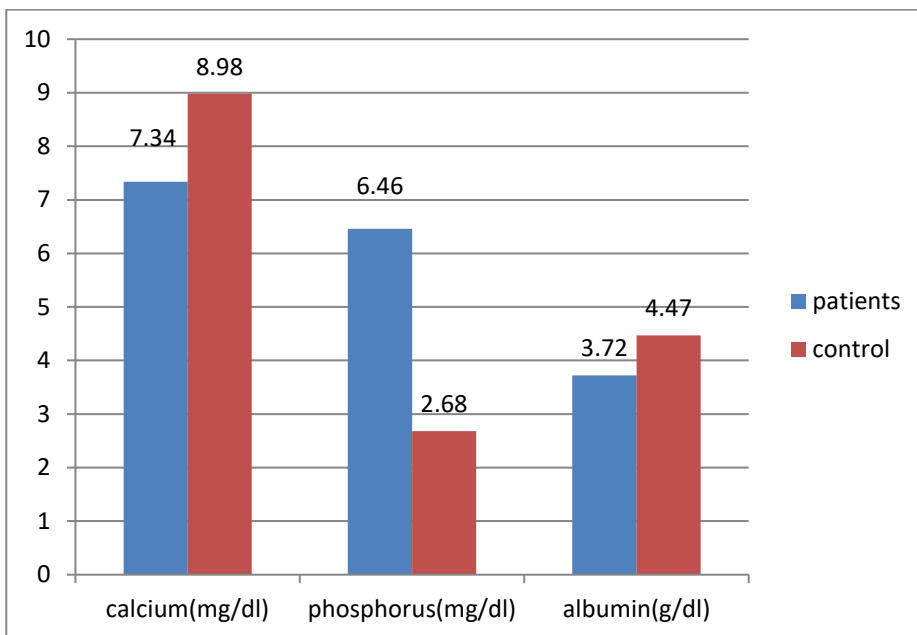


Figure 3. show differences between patients and control in calcium, phosphorus and albumin

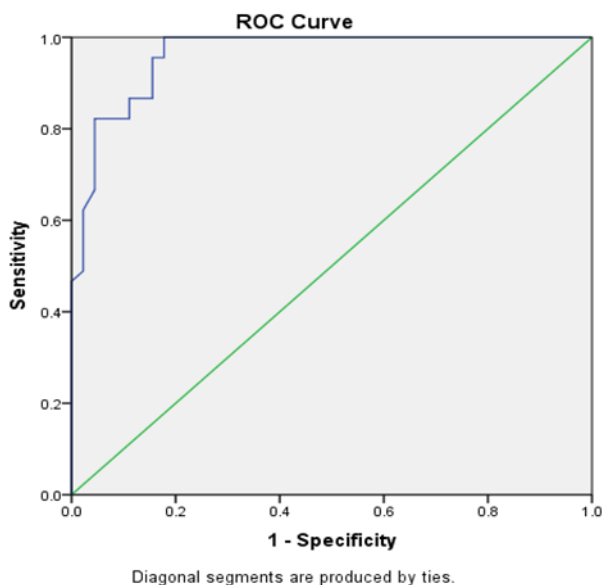


Figure 4. Criterion values and coordinates of the ROC curve analysis for OPG as differentiating patients from control subject

## Discussion

In the current study ,OPG levels increase in CKD Patients with highly significant differences ( $P \leq 0.01$ ). OPG is also implicated in metabolic bone disease and may

have a role in CKD prognosis (14). OPG levels are higher in patients with chronic renal disease(15). this result was agreed with some study in which serum OPG levels are raised in individuals with chronic renal disease, with the goal of predicting kidney function decline(16). the present study revealed that Parathyroid hormone (PTH)highly increased in CKD patients significant differences ( $P \leq 0.01$ ) when compared with control group, Fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) are hormones that regulate renal phosphate excretion and vitamin D metabolism. As renal function diminishes in chronic kidney disease (CKD), circulating FGF23 and PTH concentrations rise. (17)

Secondary hyperparathyroidism is a component of the chronic kidney disease-related mineral and bone disorders (CKD-MBD) complex, and it is associated with rapid bone turnover, ectopic calcification, and higher cardiovascular mortality. (18). This study showed phosphorus,alkaline phosphatase were higher significantly increased in patient group compare with healthy control where ( $P \leq 0.01$ ), renal osteodystrophy in a CKD patient, could result in a considerable rise in the ALP bone isoenzyme (b-ALP) This contributed to elevated ATLP levels in the blood. Actually, Higher ALP levels have been linked to an increased risk of mortality. in pre-dialysis CKD in addition to patients undergoing constant haemodialysis (19) Combination of elevated alkaline phosphatase with high PTH indicated a effective diagnostic predictive value of high-turnover bone disease (20). The biochemical changes of CKD-MBD include raised fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH), declined (1,25D), raised serum P, and decreased serum Ca. (21) Albumin was significantly ( $p \leq 0.01$ ) lower in CKD compared to control. Albumin is commonly considered as a nutritional status-assessing biological marker. Hypoalbuminemia can be caused by a variety of factors, including lossing via gastrointestinal tract or the kidney (22).

### **Conclusion**

Our findings suggest that Patients with CKD had greater levels of OPG, ALP, parathyroid hormone, and Phosphors ,The OPG, ALP and parathyroid hormone have a Beneficial association.to indicates bone mineralization status. OPG, could be used as a prognostic marker in individuals with chronic kidney disease to predict the development of bone mineral disease,The high prevalence of CKD in middle & old age, CKD patients were lower plasma Ca & albumin than healthy controls,which negatively correlated with disease activity

### **Ethical Clearance**

The Research Ethical Committee at scientific research by ethical approval of Both environmental and health and higher education and scientific research ministries in Iraq.

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