



ORIGINAL ARTICLE

**Serum Osteoprotegerin: Can It Predict Chronic Kidney Disease Among Hypertensives?**

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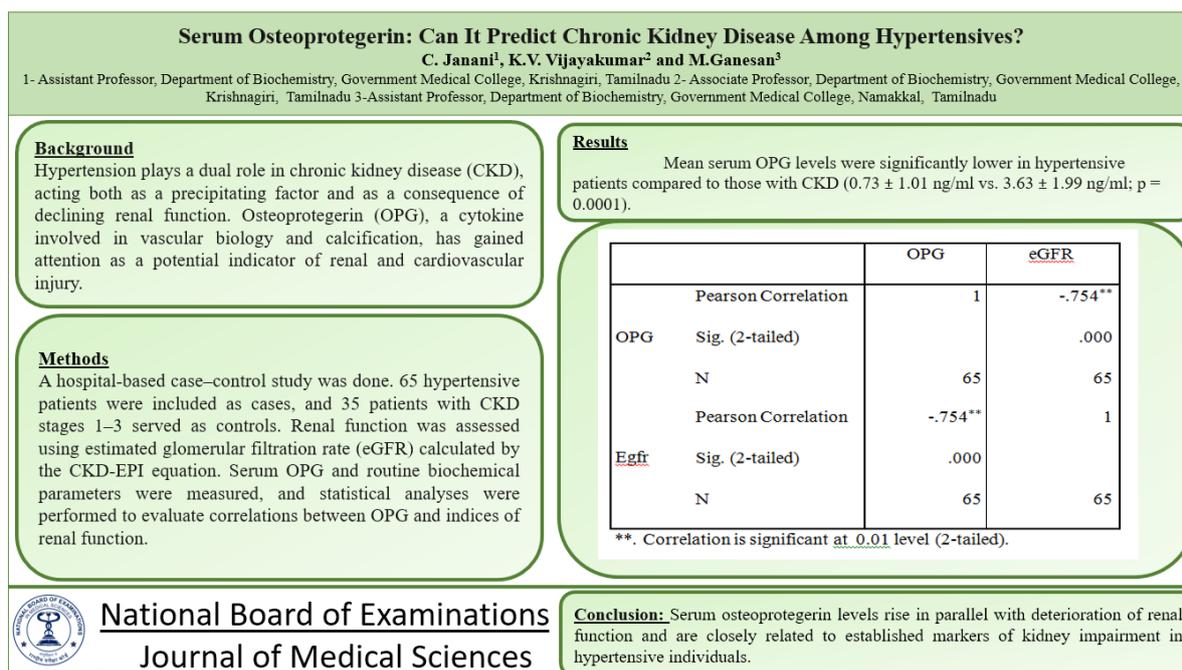
**Abstract**

**Background:** Hypertension plays a dual role in chronic kidney disease (CKD), acting both as a precipitating factor and as a consequence of declining renal function. Early renal impairment in hypertensive individuals is often clinically silent, and conventional markers may fail to detect subtle changes. Osteoprotegerin (OPG), a cytokine involved in vascular biology and calcification, has gained attention as a potential indicator of renal and cardiovascular injury. **Objectives:** To evaluate the association between serum osteoprotegerin levels and renal dysfunction in hypertensive patients, and to assess whether elevated OPG can serve as an early predictor of chronic kidney disease in this population. **Methods:** A hospital-based case-control study was carried out at Government Mohan Kumaramangalam Medical College Hospital, Salem, from December 2018 to November 2019. Sixty-five hypertensive patients were included as cases, and 35 patients with CKD stages 1–3 served as controls. Renal function was assessed using estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI equation. Serum OPG and routine biochemical parameters were measured, and statistical analyses were performed to evaluate correlations between OPG and indices of renal function. **Results:** Mean serum OPG levels were significantly lower in hypertensive patients compared to those with CKD ( $0.73 \pm 1.01$  ng/ml vs.  $3.63 \pm 1.99$  ng/ml;  $p = 0.0001$ ). Patients with CKD had higher serum creatinine levels and lower eGFR values. A strong inverse association between OPG and eGFR was observed in both groups, along with a positive correlation between OPG and serum creatinine. Serum OPG also showed significant associations with body mass index and adverse lipid parameters, suggesting a link with both renal dysfunction and cardiovascular risk. **Conclusion:** Serum osteoprotegerin levels rise in parallel with deterioration of renal function and are closely related to established markers of kidney impairment in hypertensive individuals. These findings support the potential role of OPG as an early biomarker for renal involvement and cardiovascular risk stratification in patients with hypertension.

**Keywords:** Hypertension, Chronic kidney disease, Osteoprotegerin, Estimated glomerular filtration rate, Renal impairment, Cardiovascular risk

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## Graphical Abstract



## Introduction

Chronic kidney disease (CKD) is a major global public health problem, affecting millions of people worldwide and placing a significant burden on healthcare systems due to high morbidity, mortality, and economic costs [1,2]. The Global Burden of Disease Study 2023 reports a steady rise in CKD prevalence across all regions and age groups, highlighting its growing global impact [3]. This increasing burden emphasizes the importance of early detection and preventive strategies, especially in populations at high risk.

Hypertension is one of the most important modifiable risk factors for the development and progression of CKD. The relationship between hypertension and CKD is bidirectional, with each condition worsening the other [4]. The KDIGO 2021 Clinical Practice Guideline highlights the close link between blood pressure control and kidney disease, stressing that effective management of hypertension is essential to prevent CKD progression [5]. Although

several treatment strategies are available for managing hypertension in CKD patients [6], it remains difficult to identify individuals who are at the highest risk before significant kidney damage has occurred.

In India, the burden of CKD is particularly concerning. Community-based studies and systematic reviews show a high prevalence of CKD, with many cases remaining undiagnosed until advanced stages of the disease [7]. Late diagnosis reduces the scope for early intervention and highlights the need for reliable biomarkers that can predict CKD in vulnerable individuals. Conventional markers of kidney function often detect disease only after substantial nephron loss, making it necessary to explore novel predictive indicators.

Osteoprotegerin, a glycoprotein involved in bone metabolism and vascular calcification, has recently emerged as a potential biomarker in CKD. Its association with vascular health and its elevated levels

in cardiovascular and renal disorders suggest that it may reflect early kidney dysfunction.

Given the strong association between hypertension and CKD, assessing whether serum osteoprotegerin can predict CKD among hypertensive patients is clinically relevant. If proven effective, osteoprotegerin could help in risk stratification by identifying hypertensive individuals who require closer follow-up and more aggressive treatment. This study aims to evaluate the predictive value of serum osteoprotegerin for detecting CKD in hypertensive patients, with the goal of improving early diagnosis and long-term outcomes in this high-risk population.

### **Aims and Objectives**

1. To evaluate the association between OPG and renal dysfunction in hypertensive patients and
2. To evaluate whether, the increase in serum OPG levels, could be an early predictor of Chronic kidney disease among the hypertensive patients.

### **Study Methodology**

A case-control study was conducted at Government Mohan Kumaramangalam Medical College Hospital, Salem, from December 2018 to November 2019, after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrollment.

The study included 65 patients with hypertension as cases and 35 patients with chronic kidney disease (CKD) stages 1–3 attending the Nephrology outpatient department as controls; CKD group was included as a comparison (positive control) group rather than as a true control group because CKD is a well-established clinical

condition known to be associated with the pathophysiological mechanisms under investigation. CKD stages 4 and 5 were excluded. Hypertensive cases were further categorized based on duration of hypertension into <5 years and 5–10 years. CKD staging was performed according to KDOQI guidelines using estimated glomerular filtration rate (eGFR), calculated by the CKD-EPI formula.

Controls were identified based on clinical features and routine investigations, with eGFR ranging from 45 to 90 ml/min/1.73 m<sup>2</sup>. Detailed clinical evaluation and specimen collection were performed for all participants. Inclusion criteria comprised age 30–65 years, treated hypertension, and CKD stages 1–3, while patients with diabetes, irregular antihypertensive use, systemic or congenital renal disease, and advanced CKD were excluded.

For the association between serum OPG and renal dysfunction (eGFR) And For evaluating OPG as an early predictor of CKD among hypertensive patients ( $r \approx -0.75$ ,  $n = 65$ ,  $\alpha = 0.05$ ), the post-hoc statistical power exceeded 99%. Accordingly, the sample size employed in the study is adequate and statistically justified to reliably test and address the stated study hypotheses.

### **Results**

A total of 100 participants were evaluated, comprising 65 cases and 35 controls. The mean age was comparable between the two groups, with cases having a mean age of  $55.5 \pm 8.7$  years and controls 53.6 years. The average duration of hypertension was longer among cases (4.3 years) than controls (3.0 years). Mean blood sugar levels were modestly higher in cases ( $106.0 \pm 26.17$  mg/dl) compared to

controls (93.8 mg/dl). Blood urea levels were lower in cases (25.7 mg/dl) than controls (51.8 mg/dl). Serum creatinine showed a significant difference, being lower in cases ( $1.11 \pm 0.24$  mg/dl)

compared to controls ( $1.74 \pm 0.53$  mg/dl), while eGFR was correspondingly higher in cases ( $66.0 \pm 16.13$  ml/min/1.73 m<sup>2</sup>) than controls ( $44.1 \pm 13.09$  ml/min/1.73 m<sup>2</sup>). (Table 1).

Table 1. Descriptive Data of Cases and Controls

S. No	Parameters	Cases (n=65) mean $\pm$ SD	Controls (n=35) mean $\pm$ SD
1.	Age	55.5 $\pm$ 8.7	53.6 $\pm$ 7.1
2.	Hypertension duration	4.3 $\pm$ 3.7	7.9 $\pm$ 3.0
3.	Blood sugar (mg/dl)	106.0 $\pm$ 26.17	93.8 $\pm$ 13.83
4.	Blood urea (mg/dl)	25.75 $\pm$ 5.7	51.86 $\pm$ 8.97
5.	Sr. Creatinine (mg/dl)	1.11 $\pm$ 0.24	1.74 $\pm$ 0.53
6.	Total cholesterol (mg/dl)	205.1 $\pm$ 34.52	263.4 $\pm$ 50.81
7.	Triglycerides (mg/dl)	218.9 $\pm$ 84.54	191.4 $\pm$ 44.44
8.	HDL(mg/dl)	46.82 $\pm$ 8.74	40.49 $\pm$ 4.80
9.	LDL(mg/dl)	114.5 $\pm$ 33.91	184.7 $\pm$ 47.02
10.	Sr. Calcium(mg/dl)	8.52 $\pm$ 1.42	7.90 $\pm$ 0.95
11.	Sr.Uric acid (mg/dl)	4.50 $\pm$ 1.08	4.89 $\pm$ 0.77
12.	Total protein(g/dl)	6.59 $\pm$ 0.78	6.81 $\pm$ 0.53
13.	Albumin(g/dl)	3.47 $\pm$ 0.48	3.66 $\pm$ 0.48
14.	eGFR	66.01 $\pm$ 16.13	44.16 $\pm$ 13.09
15.	OPG (ng/dl)	0.73 $\pm$ 1.01	3.63 $\pm$ 1.99

Analysis of lipid parameters revealed that cases had significantly lower total cholesterol levels ( $205.1 \pm 34.52$  mg/dl) compared to controls ( $263.4 \pm 50.81$  mg/dl). Triglyceride levels were higher in

cases ( $218.9 \pm 84.54$  mg/dl) than controls ( $191.4 \pm 44.44$  mg/dl). HDL cholesterol was higher among cases ( $46.8 \pm 8.74$  mg/dl) compared to controls ( $40.4 \pm 4.80$  mg/dl), whereas LDL cholesterol levels were

markedly lower in cases ( $114.5 \pm 33.91$  mg/dl) than in controls ( $184.7 \pm 47.02$  mg/dl). Serum calcium levels were higher in cases ( $8.52 \pm 1.42$  mg/dl) compared to controls ( $7.90 \pm 0.95$  mg/dl). Serum uric acid levels were comparable between groups ( $4.50 \pm 1.08$  mg/dl in cases and  $4.89$  mg/dl in controls). Total protein and albumin values were slightly lower in cases ( $6.59$  g/dl and  $3.47$  g/dl, respectively) than controls ( $6.81$  g/dl and  $3.66$  g/dl).

Sex distribution differed between groups, with a male predominance among controls

(24 males, 11 females) and a higher proportion of females among cases (37 females, 28 males). Serum osteoprotegerin levels showed a pronounced and statistically significant reduction in cases ( $0.734 \pm 1.017$  ng/ml) compared to controls ( $3.638 \pm 1.995$  ng/ml;  $p = 0.0001$ ). (Table 2) Statistically significant differences ( $p = 0.0001$ ) were also observed between groups for serum creatinine, total cholesterol, triglycerides, HDL, LDL, and calcium.

Table 2. Statistical analysis of serum osteoprotegerin in control and cases

<b>OSTEOPROTEGERIN ng/ml</b>	<b>N</b>	<b>MEAN</b>	<b>SD</b>	<b>INFERENCE</b>
CONTROLS	35	3.638	1.995	P= 0.0001
CASES	65	0.734	1.017	P<0.05

Table 3, shows that Correlation analysis among cases demonstrated a strong inverse relationship between serum osteoprotegerin and eGFR ( $r = -0.754$ ,  $p < 0.01$ ), along with significant positive correlations with serum creatinine ( $r = 0.709$ ), BMI ( $r = 0.246$ ), total cholesterol ( $r = 0.321$ ), and LDL cholesterol ( $r = 0.340$ ). In controls, serum osteoprotegerin similarly showed an inverse correlation with eGFR ( $r = -0.754$ ,  $p < 0.01$ ) and positive correlations with creatinine ( $r = 0.551$ ),

total cholesterol ( $r = 0.566$ ), triglycerides ( $r = 0.661$ ), and LDL cholesterol ( $r = 0.471$ ).

Figure:1 Receiver Operating Characteristic (ROC) curve evaluating the diagnostic performance of the test parameter. The area under the ROC curve (AUC) was 0.9378, indicating excellent discriminatory ability. The standard error was 0.02337, suggesting good precision of the AUC estimate, which was statistically Significant (P value  $< 0.001$ )

Table 3: Pearson's correlation analysis of OPG and eGFR in cases

		OPG	<u>eGFR</u>
OPG	Pearson Correlation	1	-.754**
	Sig. (2-tailed)		.000
	N	65	65
<u>Egfr</u>	Pearson Correlation	-.754**	1
	Sig. (2-tailed)	.000	
	N	65	65

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

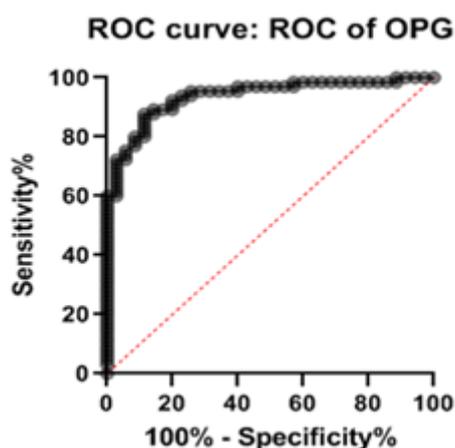


Figure 1. Receiver Operator Characteristic Curve

## Discussion

The present case-control study evaluated the relationship between serum osteoprotegerin (OPG), renal function, and cardiovascular risk factors among hypertensive patients and individuals with chronic kidney disease (CKD) stages 1–3. The results demonstrate that serum OPG levels were significantly higher in CKD patients compared to hypertensive cases, with a parallel decline in estimated glomerular filtration rate (eGFR) and

elevation in serum creatinine, highlighting progressive renal dysfunction. These findings reinforce the role of OPG as a biomarker associated with renal impairment.

Hypertension is both a causative and contributory factor in the progression of CKD. In the present study, declining eGFR was significantly associated with worsening hypertension, supporting previous observations that blood pressure burden increases as renal function

deteriorates. Li et al. [9] reported that even prehypertension increases the risk of developing CKD, emphasizing the importance of early blood pressure control to prevent renal damage. The strong inverse correlation between serum OPG and eGFR observed in both hypertensive and CKD groups in this study further supports the hypothesis that OPG reflects renal functional decline.

Serum OPG levels showed a significant negative correlation with eGFR and a positive correlation with serum creatinine, total cholesterol, LDL cholesterol, triglycerides, and BMI. Similar findings have been reported by Schoppet et al. [8] who demonstrated that elevated OPG levels reflect vascular injury and inflammatory processes rather than bone metabolism alone. The progressive rise in OPG with worsening renal function suggests its involvement in vascular remodeling and endothelial dysfunction commonly seen in CKD.

Dyslipidemia was prominent among CKD patients in the present study, characterized by elevated total cholesterol, LDL cholesterol, and triglycerides, along with reduced HDL cholesterol. These findings are consistent with studies by Tsimihodimos et al. [10] and Vaziri et al [11], who described profound disturbances in lipoprotein metabolism in CKD, contributing to accelerated atherosclerosis and renal microvascular injury. The coexistence of hypertension and dyslipidemia further amplifies cardiovascular risk, as highlighted by Ariyanti et al. [12] and Dalal et al. [13] who described the concept of “lipitension” linking metabolic and vascular pathology.

Linear regression analysis in hypertensive patients revealed a significant inverse relationship between OPG and

eGFR, indicating that OPG may serve as an independent predictor of renal dysfunction, consistent with the findings of Bernardi et al. [14]. Furthermore, receiver operating characteristic curve analysis demonstrated excellent diagnostic accuracy of OPG in differentiating hypertensive patients from CKD patients, with high sensitivity and specificity. These findings are in concordance with Lee et al. [15] who identified serum OPG as an independent predictor of cardiovascular events and mortality in CKD patients.

Overall, the present study supports the utility of serum OPG as an early biomarker for renal dysfunction and cardiovascular risk stratification among hypertensive patients, warranting its consideration in clinical assessment and future longitudinal studies.

### **Conclusion**

The present study demonstrates that serum osteoprotegerin (OPG) levels increase with worsening renal function and show a significant inverse relationship with estimated glomerular filtration rate in hypertensive patients. Elevated OPG levels were associated with higher serum creatinine and adverse lipid profile, reflecting underlying vascular and renal dysfunction. These findings suggest that OPG may serve as an early biomarker for decline in renal function and cardiovascular risk among hypertensive individuals. Early identification of renal involvement using OPG may facilitate timely intervention and improve clinical outcomes.

### **Limitation**

Lack of a “True” Healthy Control: The study lacks a group of healthy, non-hypertensive, non-CKD individuals. Without a healthy baseline, it is difficult to

determine if the hypertensive “cases” already have elevated OPG compared to the general population. **Selection Bias:** The CKD controls were recruited from a Nephrology outpatient department. These patients might have other comorbidities or medications not present in the hypertensive group, which could confound the OPG levels.

### Author Contributions

Author 1 has contributed to the conceptualization and definition of the intellectual content of the manuscript, design of the study and Manuscript preparation. Author 2 contributed to the literature search, manuscript editing, and manuscript review. Author 3 contributed towards data acquisition Statistical analysis, Manuscript review and editing. Author 1 will act as the corresponding author of the manuscript

### Data availability

The datasets generated and analysed in this study are available from the corresponding author on reasonable request. They are not publicly shared because they contain sensitive information that could indirectly identify participants.

### Ethical Approval

This study has been approved by the Institution Ethics Committee Ref. No: GMCKMC&H/4341/IEC/02/2018-74

### Informed Consent

Written informed consent was obtained from all participants after explaining the study procedures, potential risks and benefits. Consent covered both participation and publication of anonymised findings, with assurance of confidentiality and data privacy.

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