SERUM OSTEOPROTEGERIN IS A PREDICTOR OF DIASTOLIC DYSFUNCTION AND VASCULAR STIFFNESS IN CHRONIC KIDNEY DISEASE PATIENTS

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Background and Aim

- Osteoprotegerin (OPG) is a cytokine that regulates bone resorption and is implicated in the process of vascular calcification and stiffness. Human studies have demonstrated associations between higher serum ostoeprotegerin levels and adverse cardiovascular outcomes in CKD patients (1).
- The aim of the present study is to evaluate the association between osteoprotegerin and fibroblast growth factor 23 (FGF23) concentrations with respect to vascular stiffness and cardiac disease in chronic kidney disease (CKD) patients.

Methods:

- We prospectively enrolled 44 consecutive patients with CKD in pre-dialysis (mean age 67.8 ± 8.4 years, 22 men). For a subgroup of 10 patients we enrolled 10 age- and gender-matched normal subjects. The stage of CKD has been established based on the estimated glomerular filtration rate (eGFR) using CKD-EPI formula.
- ***Laboratory tests***: OPG, FGF23, intact parathyroid hormone (iPTH) were measured using xMAP technology (Luminex® 200™).
- ***Aortic pulse wave velocity (PWV)*** was measured using the SphygmoCor (AtCor Medical, Australia) device. Measurements were made using the right carotid and femoral arteries with patients in the supine position.
- ***Echocardiographic evaluation*** was performed using the Vivid 7 ultrasound system, General Electric. End-systolic and end-diastolic volumes were used to calculate left ventricular (LV) ejection fraction (EF) by Simpson biplane method. Impaired LVEF was defined as <45%. Left ventricular filling pressures were assessed using the E/septal E' ratio. Diastolic function was assessed using several parameters including E/A ratio, deceleration time of early filling velocity (DT)and left atrial volume (2). LV mass was calculated using the formula: LV mass (in grams) = 0.8 x {1.04 [(LV internal dimension + septal wall thickness + posterior wall thickness)^3 – LV internal dimension^3]} + 0.6. LV mass was indexed to height$^{2.7}$ (3). Valvular calcification was defined as bright echoes of more than 1 mm on 1 or more cusps of the aortic and the mitral valves.
- ***Statistical analysis*** was performed using IBM SPSS Statistics Version 21.

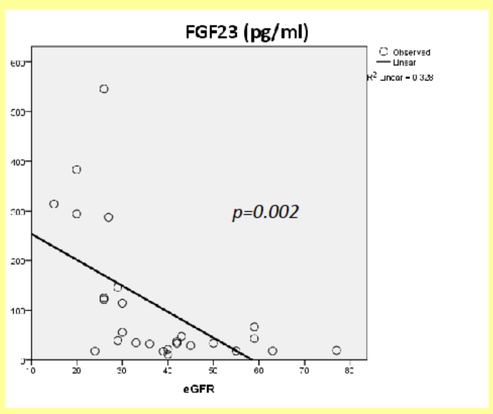
Results:

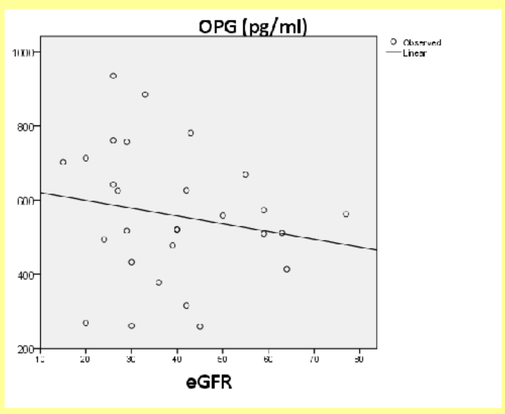
- The etiology of CKD was: diabetic nephropathy (19 pts), nephroangiosclerosis (19 pts), tubulointerstitial nephropathy (9 pts).
- - 8 patients CKD stage 2
  - 24 patients CKD stage 3
  - 12 patients CKD stage 4.

  The mean eGFR was 38.9 ± 15.5 ml/min/1.73m^2.
- When compared to healthy controls, CKD patients had elevated levels of OPG FGF23, iPTH and significantly higher LV mass, E/septalE' ratio and PWV.

	CKD patients	Controls	*P value*
OPG (pg/ml)	563.1 ± 176.7	240.1 ± 132.5	*0.02*
FGF23 (pg/ml)	106.8 ± 134.3	9.5 ± 0.8	*0.001*
iPTH (pg/ml)	67.7 ± 49.5	35.2 ± 20.3	*0.04*
PWV (m/s)	10 ± 2.3	7.5 ± 1.7	*0.03*
LVMI g/m^2	121.7 ± 37.8	84 ± 13.1	*0.002*
E/septalE' ratio	12.2 ± 3.5	7.9 ± 1.8	*0.001*

- The levels of FGF23 inversely correlated with eGFR. We observed progressively higher serum OPG levels with lower eGFR.

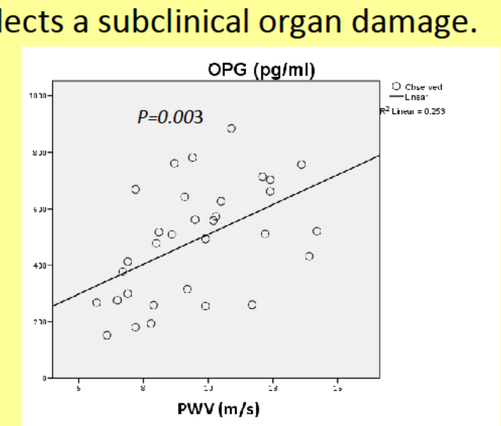




- Diastolic dysfunction was present in 89.3% pts, left ventricular hypertrophy in 72.2%, and aortic valve calcifications were present in 58.2% pts.

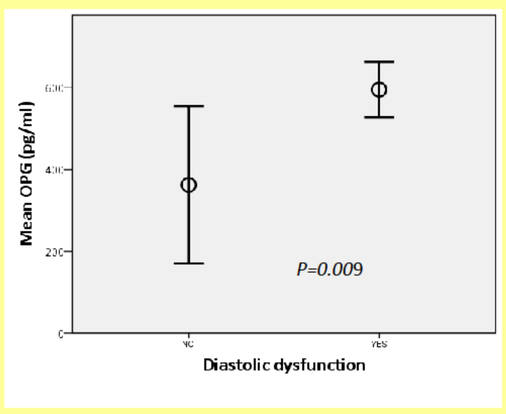
Arterial stiffness

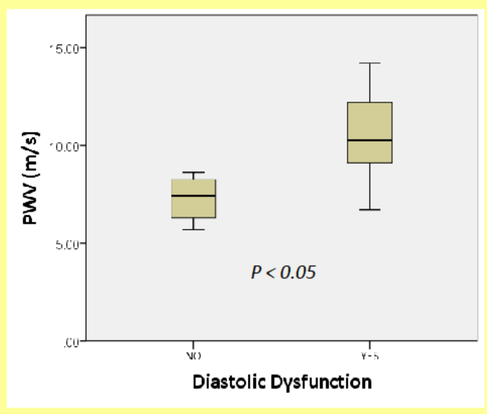
- With use of linear regression, higher serum OPG was associated with higher aortic pulse wave velocity (p =0.003). We didn't find significant correlation between FGF23 and PWV. Though, FGF23 was significantly increase in patients with PWV ≥ 12 m/s, which reflects a subclinical organ damage.
- **A stepwise multiple regression** analysis of model 1 revealed that **PWV correlated independently with the OPG level** (beta =0.737, p=0.003).



Diastolic dysfunction

- OPG levels significantly correlated with diastolic dysfunction (p=0.009).
- Also, PWV significantly correlated with diastolic dysfunction (p< 0.05).
- FGF23 correlated with aortic valvular calcifications (p=0.01).





- Furthermore, a stepwise multiple regression analysis of model 1 revealed that E/septalE' showed an independent correlation with OPG, eGFR, aortic pressure and VS ejection duration.

Conclusions:

- **Our results demonstrated that osteoprotegerin is correlated with increased vascular stiffness and diastolic dysfunction in CKD patients.**
- **Our data underscore that cardiovascular disease appear even from early stages of CKD and mineral-bone disease serology parameters could be used as surrogate biomarkers for cardiac complications among patients with CKD.**

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