Bone Specific Alkaline Phosphatase and Cardiovascular Morbidity among Patients on Maintenance Hemodialysis

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Abstract: Background: Vascular calcification is common in individuals with chronic kidney disease (CKD) and significantly correlated to the high cardiovascular death risk. In advanced CKD, stages 3 through 5, secondary hyperparathyroidism (SHPT), along with renal osteodystrophy, are common and may be associated with abnormal mineral metabolism and / or abnormal serum or tissue mineral levels, vascular calcification, and poor survival, especially among those who undergo maintenance dialysis treatment. Serum alkaline phosphatase (ALP) is a biochemical marker of bone turnover and is used to monitor metabolic bone disease associated with renal insufficiency. Higher levels of serum ALP were associated with vascular calcification in maitenance hemodialysis patients MHD. Bone-specific ALP (bALP) is a byproduct of osteoblasts and is a more specific measure of bone formation as well as bone turnover and is increased in MHD patients, probably as a result of high turnover bone disease. Atherosclerosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. Inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) may provide an adjunctive method for global assessment of cardiovascular risk. **Objectives of this work:** (1) Estimate the clinical utility of serum biomarkers of bone metabolism like ALP, bALP, intact parathyroid hormone, calcium, and phosphorus as potential markers and indicators in diagnosis of renal osteodystrophy in MHD patients aiming to improve their clinical outcomes. (2) Evaluate the association between renal osteodystrophy and progression of vascular calcification detected by echocardiography and carotid Duplex in MHD patients. (3) Testing the role of CRP and hsCRP in mediating the increased cardiovascular risk in MHD patients. **Patients and methods:** Seventy MHD patients and 15 healthy volunteers were enrolled in the study. All patients and controls were subjected to echocardiography, carotid duplex and predialysis blood sampling for estimation of routine blood chemistry (Calcium, Phosphorus, urea, creatinine, glucose, albumin, ALT, AST, ALP, cholesterol, triglyceride, HDLc), intact parathormone (iPTH) and hsCRP. Bone specific alkaline phosphatase (bALP) was also measured. **Results**: Plasma levels of ALP, bALP, iPTH, CRP, hs-CRP, urea, creatinine, glucose, phosphorus, were significantly higher in MHD group compared to control group. Statistical analysis revealed highly significance statistical difference in EDD, ESD, EF, IVS, PWT, IMT in MHD group compared to the control group. Mitral valve and aortic valve calcification was found in 27.4%, 71.4% respectively in hemodialyzed patients. b-ALP sensitivity, specificity and positive predictive value of the test at a cut off > 10 IU/L were found to be 89%, 67% and 79% respectively. ***Conclusion:*** Plasma bALP can be measured with a reliable immunoassay in hemodialysis patients represents a highly sensitive and specific biochemical marker of skeletal remodeling in these patients, even better when associated with plasma iPTH levels. Abnormal mineral metabolism and inflammation are pivotal factors for the increased cardiovascular risk in CKD patients.

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1. Introduction

Vascular calcification is common in individuals with CKD and significantly correlated to the high cardiovascular death risk (1). Both intimal and medial calcification is observed frequently in patients with CKD (2,3). Several mechanisms have been implicated for the high prevalence of vascular calcification in CKD, inducing the high burden of conventional cardiovascular risks such as diabetes, hypertension, and dyslipidemia; bone and mineral disorders such as calcium load and secondary hyperparathyroidism and chronic inflammation (4).

In advanced CKD, stages 3 through 5, secondary hyperparathyroidism (SHPT), along with renal osteodystrophy, is common and may be associated with abnormal mineral metabolism and / or abnormal serum or tissue mineral levels, vascular calcification, and poor survival, especially among those who undergo maintenance dialysis treatment (5).

Serum ALP is a biochemical marker of bone turnover and is used to monitor the metabolic bone disease associated with renal insufficiency. Higher serum levels of minerals and higher ALP levels, were associated with increased all- cause death risk in a 2-year cohort of 58,000 MHD patients (5).

Experimental studies suggested that alkaline phosphatase might promote vascular calcification (6). Indeed, higher levels of serum alkaline phosphatase were independently associated with progressive arterial calcification in a longitudinal study of stage IV and V (CKD) patients (7).

Clinical studies have found serum ALP to be associated with coronary artery calcification and all-cause mortality in patients with CKD and on hemodialysis (8, 9).

Bone-specific ALP is a by-product of osteoblasts and is a more specific measure of bone formation as well as bone turnover (8). Bone-specific alkaline phosphatase (bALP) is increased in MHD patients, probably as a result of high turnover bone disease. Indeed, a statistical association between bALP level and the presence of aortic calcification are present in patients with osteoporosis (10). Similarly, in vivo study showed an increased level of circulating bALP in patients with CKD in presence of aortic calcification (11).

Apart from vascular calcification, inflammation is another potential mechanism for the association between higher serum alkaline phosphatase levels and increased mortality. Laboratory and experimental evidence indicate that atherosclerosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process (12). Thus, researchers have hypothesized those inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) may provide an adjunctive method for global assessment of cardiovascular risk (13). Plasma levels of hsCRP have been associated with increased vascular event rates (14). Mendall *et al*., 2000 (15) demonstrated the association between hsCRP and all-cause mortality. Several large-scale prospective studies demonstrated that hsCRP is a strong independent predictor of future myocardial infarction and stroke among apparently healthy men and women. Pasceri et *al*., 2000 (16) described CRP within atheromatous plaque, as a correlate of endothelial dysfunction, and as having a direct role in cell adhesion molecular expression that raised the possibility that CRP may also be a potential target for therapy. Highly sensitive hsCRP has the potential to play an important role as an adjunct for global risk assessment in primary prevention of cardiovascular disease (14).

Aim of the Work:

1. Estimate the clinical utility of serum biomarkers of bone metabolism like ALP, bALP, intact parathyroid hormone, calcium, and phosphorus as potential markers and indicators in diagnosis of renal osteodystrophy in MHD patients aiming to improve their clinical outcomes.
2. Evaluate the association between renal osteodystrophy and progression of vascular calcification detected by echocardiography and carotid Duplex in MHD patients.
3. Testing the role of CRP and hsCRP in mediating the increased cardiovascular risk in MHD patients.

2. Methods:

Seventy adult uremic patients from dialysis unit of Theodor Bilharz Research Institute, (23 females and 47 males), were included in this study. Their mean (± SD) age was 56 ±14 years. All patients were treated by conventional hemodialysis, 3 sessions weekly, 4 hours each, for a period ranging from 7 to 10 years.

Exclusion criteria included liver diseases, ethanol or drug abuse, active malignancy and pregnancy.

Fifteen (age and sex matched) healthy control subjects, selected from medical and paramedical staff are included in this study.

All patients and controls in this study were subjected to the following:

- Full clinical examination and routine laboratory investigation.
- Electrocardiography.
- Echocardiography: Standard transthoracic M. mode, two dimensional, continuous and pulsed wave Doppler echocardiograms using 2.5 MHz transducer. All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (Sahn *et al.,* 1978).
- Carotid Duplex: Ultrasonographic studies on common carotid arteries were performed by using a 7.5 MHz high resolution probe. IMT was defined as a low-level echo gray band that does not project into the arterial lumen (Berglund, 1994) and was measured during end-diastole as the distance from the leading edge of the second echogenic line of the far walls of the distal segment of the common carotid artery, the carotid bifurcation, and the initial tract of internal carotid artery on both sides.
- Biochemistry: Predialysis blood sampling was performed after a 12-h fast. Routine chemistry (calcium, phosphorus, urea, creatinine, glucose,

albumin, ALT, AST, cholesterol, triglyceride, HDL and ALP were performed using autoanalyzer Beckman CX3 Delta analyzer. Plasma iPTH and hsCRP were measured by a solid-phase chemiluminescent enzyme-labeled immunometric assay using Immulite/ Immulite 1000. Bone ALP was measured by using a radioimmunometric assay provided by Hybritech Europe S.A. Belgium.

Statistical Analysis:

All results are given as the means ± SEM. Statistical analysis was performed comparison between two groups, parametric (*t*-test) or non-parametric (Mann–Whitney test) unpaired *t*-tests were used. The significance of the magnitude of correlation coefficients of biochemical compared with echocardiographic and duplex data was assessed by linear regression analysis. The P value was regarded significant if <0.05 at confidence interval 95%. The statistical significances 0f differences in frequencies of variants between the groups (expressed as percent) were tested using the chi-square (χ^2). Post-test probability parameters (sensitivity, specificity and predictive value positive and negative), receiver operator characteristic (ROC) curves and areas under the curves were obtained using Analyze Software for SPSS version 18.0 (Analyze software, LTD, Leeds, UK). ROC curves are a plot of the true positive rate (sensitivity) against false positive rate (1- specificity) and the area under the curve is a measure of test accuracy.

3. Results:

The demographic data of patients and controls revealed mean ages 56.1 ± 14 years and 51.6 ± 10.1 years respectively. Twenty three were females (33%) and forty seven were males (67%). Duration of hemodialysis ranged from 7-10 years with a mean 6.4±4.9 years. Systolic and diastolic blood pressure measurements ranged 80-190 mmHg with a mean 129.01 ± 19.25 and 50-110 mmHg with a mean 80.14 ±11.58 respectively in MHD group.

Plasma levels of ALP, bALP, iPTH, CRP, hsCRP, urea, creatinine, glucose, phosphorus, were significantly higher in MHD group compared to control group (P<0.001). However, Ca and albumin levels were significantly lower in MHD group when comparing the two studied group (P<0.001). No significant difference was observed for plasma level of AST, ALT, triglycerides and HDLc (Table 1 and figure 1).

Statistical analysis revealed highly statistical significant difference in echocardiographic data particularly EDD, ESD, EF, IVS, PWT, IMT in MHD group compared to the control group (Table 2).

The calcification percentage of the cardiac valves and pericardium in the studied groups are shown in (Table 3), which were significantly higher in MHD group compared to control group.

Positive correlations were found between bALP versus ALP (Figure 2) and iPTH (Figure 3) (r = 0.99), (P< 0.001), (r = 0.77) (P<0.001) respectively. However negative correlation was found between bALP and albumin (Figure 4) (r = - 0.448) (P < 0.001).

Similarly positive correlation was found between ALP and iPTH (r=0.4) (P<0.001) but ALP showed negative correlation with albumin (r= -0.35) (P <0.01).

Intact PTH showed a positive correlation with creatinine (Figure 5) (r = 0.289) (P < 0.01), and a negative correlation with albumin (r = -0.352) (P < 0.01).

Positive correlations were found between phosphorus and CRP, hsCRP and creatinine (r = 0.301) (P < 0.01), (r = 0.357) (P < 0.01) and (r = 0.478) (P < 0.001) respectively.

Posterior wall thickness showed positive correlation with ALP, bALP, iPTH and IMT (r = 0.245) (P < 0.02), (r = 0.249) (P < 0.02), (r = 0.246) (P < 0.02) and (r = 0.3) (P < 0.01) respectively.

IMT showed positive correlation with ALP, bALP, iPTH and hsCRP (r= 0.212) (p<0.05) , (r = 0.207) (P < 0.05) (r = 0.270) (P < 0.01) and (r = 0.22) (P < 0.04) respectively.

b-ALP revealed sensitivity 89%, specificity 67% and positive predictive value of the test 79% at a cut off > 10 IU/L as shown in figure (6).

However the test result variables of b–ALP and cholesterol, EDD, urea, creatinine and EF revealed area under curve 0.792,0.742 and 0.256 and significance 0.011, 0.035 and 0.033 concerning urea, creatinine and EF (Figure 7).

Table 1: Comparison Between Plasma Biochemical Parameters In The Studied Groups.

	Control group (n = 15)	MHD group (n = 70)	t-test	P value
ALP (IU/L) Range Mean±SEM	 18 – 65 45.07 ± 3.69	 20 – 330 144.20 ± 12.48	7.617	P<0.001
b-ALP (IU/L) Range Mean±SEM	 3.37 -12.85 8.84 ± 0.73	 3.85 – 110 43.73 ± 4.55	7.576	P<0.001
Ratio b-ALP/ALP Range Mean±SEM	 0.19 – 0.20 0.20 ± 0.004	 0.17 -0.34 0.27 ± 0.07	8.30	P<0.001
i PTH (pq/ml) Range Mean±SEM	 7.3 -82.7 35.60 ± 4.66	 14.80 -1746.70 437.82 ± 51.38	7.802	P<0.001
CRP (mg/L) Range Mean±SEM	 0.20 – 0.80 0.57 ± 0.033	 0.60 -4.80 0.97 ± 0.0.10	3.806	P<0.001
hsCRP (mg/L) Range Mean±SEM	 0.06 – 0.98 0.26 ± 0.06	 0 -7.20 1.07 ± 0.16	4.719	P<0.001
Urea (mg/dl) Range Mean±SEM	 15 – 42 29.50 ± 1.13	 19 – 272 117.51 ± 5.15	16.638	P<0.001
Creatinine (mg/dl) Range Mean±SEM	 0.40 – 1.20 1.23 ± 0.047	 1.7 -13.40 7.34 ± 0.31	19.34	P<0.001
Bl Sugar (mg/dl) Range Mean±SEM	 70 – 103 87.80 ± 2.6	 17 – 410 125.14 ± 9.68	3.719	P<0.001
Ca++ (mg/dl) Range Mean±SEM	 8.3 – 10.20 9.70 ± 0.18	 2.80 – 15.80 8.69 ± 0.24	3.482	P <0.001
Phosphorus (mg/dl) Range Mean±SEM	 2.50 – 4.50 3.28 ± 0.93	 1.30 – 11.50 5.36 ± 0.23	6.158	P<0.001
AST (IU/L) Range Mean±SEM	 12 – 32 21.93 ± 1.73	 5 – 51 18.50 ± 1.04	1.697	NS
ALT (IU/L) Range Mean±SEM	 18 – 35 24.80 ± 1.35	 5 – 48 21.93 ± 1.14	1.624	NS
Albumin (g/L) Range Mean±SEM	 3.60 – 4.30 2.20 ± 0.13	 1.2-4.3 2.86 ± 0.09	6.128	P <0.001
Cholesterol (mg/dl) Range Mean±SEM	 95 – 155 129.13 ± 4.18	 85 – 250 147.63 ± 5.16	2.784	P <0.001
TG (mg/dl) Range Mean±SEM	 77 – 127 101.33 ± 3.65	 15 – 928 117.73 ± 14.90	1.157	NS
HDLc (mg/dl) Range Mean±SEM	 35 – 43 38.73 ± 3.10	 30 – 49 37.56 ± 4.37	1.197	NS

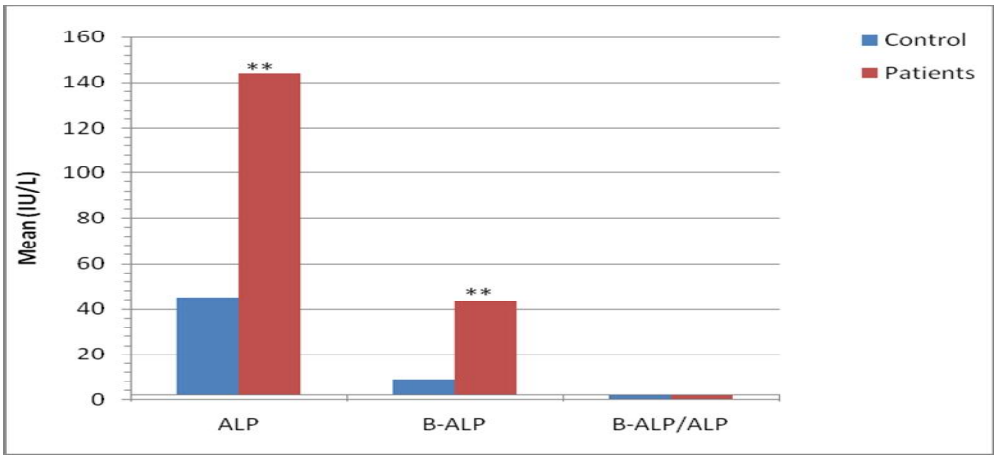


Figure (1) Comparison between ALP, b-ALP and b-ALP/ALP in the studied groups.

Table (2): Descriptive Statistics of Echocardiographic and Duplex Data of Studied Groups.

	Controls (n=15) Mean±SEM	Patients (n=70) Mean±SEM	U-test	P value
EDD	42.1 ± 1.29	49.8 ±1.04	4.65	P<0.001
ESD	26.6 ± 1.3	33.4 ± 0.63	4.99	P<0.001
IVS	8.9 ± 0.3	11.6 ± 0.27	6.83	P<0.001
PWT	8.9 ± 0.28	11.1 ± 0.11	6.68	P<0.001
EF	68.2 ± 1.4	63.1 ± 1.2	2.69	P<0.013
IMT	0.79 ± 0.03	1.11 ± 0.08	3.59	P<0.001

EDD: End diastolic diameter ESD: End systolic diameter
IVS: Interventricular septum PWT:Posterior wall thickness
EF: Ejection fraction IMT: Intima media thickness

Table (3): The calcification of cardiac valves and pericardium of the studied groups

	Patients (n=70)	Controls (n=15)	χ^2	P value
Aortic valve	50 (71.4%)	2 (10%)	15.1	0.05
Mitral valve	15 (27.4%)	1 (5%)	0.93	NS
Pericardium	60 (85.7%)	2 (10%)	29.2	0.01

Table (4):The correlation between different parmeters

	PWT	iPTH	IMT	Albumin	bALB	hsCRP	CRP	Creatinine
Phosphorus						r=0.357 P<0.002	r=0.3 P0.01	r=0.478 P<0.001
iPTH	r= 0.246 P<0.02			r=-0.35 P<0.01				r= 0.289 P<0.01
IMT	R=0.3 P<0.01	r = 270 P<0.01				r=0.22 P<0.04		
bALB	r=0.249 P<0.02	r=0.77 P<0.001	r=0.207 P<0.05	r=-0.448 P<0.001				
ALP	r= 0.245 P<0.02	r=0.4 P<0.001	R=0.212 P<0.05	r = -0.35 P<0.003	r=-0.99 P<0.001			

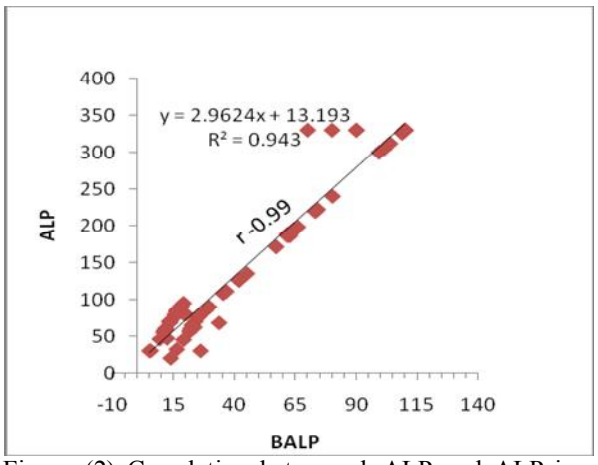


Figure (2) Correlation between b-ALP and ALP in MHD patients

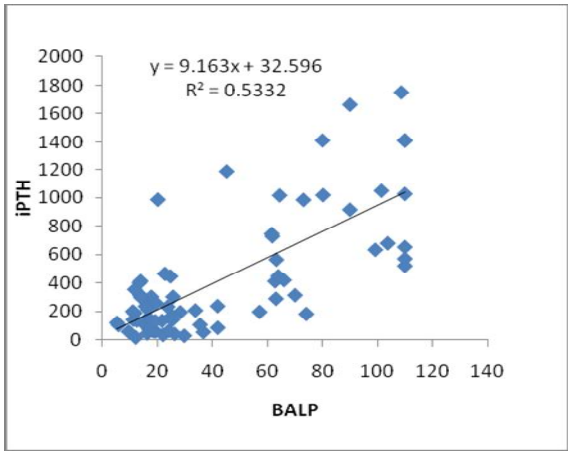


Figure (3) Correlation between b-ALP and i-PTH in MHD patients.

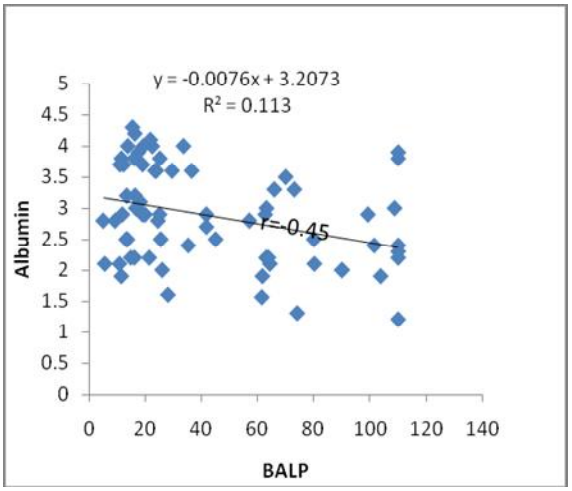


Figure (4) Correltion between b-ALP and albumin in MHD group.

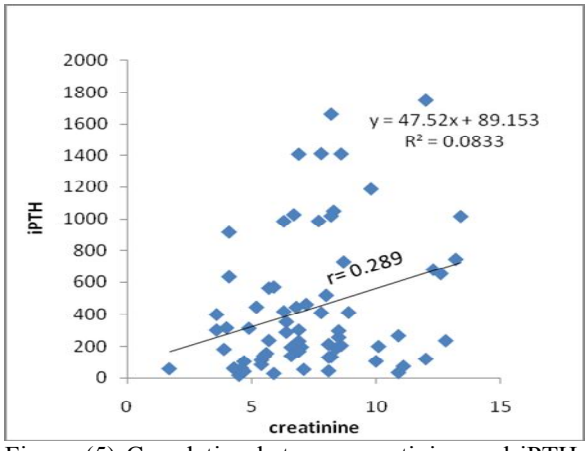


Figure (5) Correlation between creatinine and iPTH in MDH group.

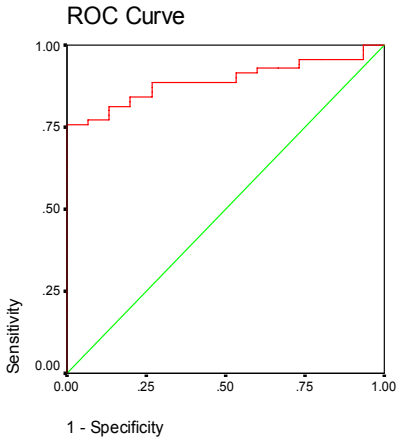
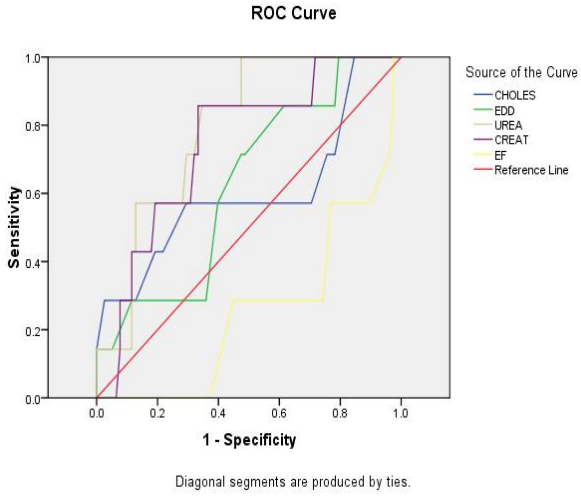


Figure (6) ROC curve of b-ALP



Figure(7) ROC curve b-ALP and cholesterol, EDD, urea, creatinine and EF.

4. Discussion:

In advanced chronic kidney disease (CKD; stage 3 through 5), secondary hyperparathyroidism (SHPT), along with renal osteodystrophy is common and may be associated with abnormal mineral metabolism and / or abnormal serum or tissue mineral levels, vascular calcifications and poor survival especially among those who undergo maintenance dialysis treatment (17). Progression of vascular calcification closely parallels bone loss, (18).

In the current study plasma levels of ALP, bALP and iPTH are significantly higher in MHD group compared to control group (P<0.001). This coincides with study of (19) who reported that: Serum ALP concentration is usually increased in renal osteodystrophy, especially in high-turnover bone disease (19). The KDOQI guidelines state that the deleterious effects of high serum PTH levels may be manifested by elevated b-ALP activity as a result of associated bone resorption (20).

The magnitude of bALP enzyme elevation may indeed be a more reliable marker of severity of the high-turnover osteodystrophy than increased PTH levels, especially because the circulating serum bALP originates directly from the pathologic bone system. Consistent with the foregoing motion, a meta-analysis showed that the treatment of renal osteodystrophy by means of vitamin D analogs can effectively decrease bALP, even through such a treatment may not decrease serum PTH consistently (21), hence the reported link between vitamin D analogs and improved survival in CKD may be via the bALP pathway (22).

Bone-specific ALP (bALP) is secreted by osteoblast cells, and it is thought that bALP plays a major role in bone formation and skeletal mineralization .It is increased in MHD patients, probably as a result of high-turnover bone disease (11); indeed, a statistical association between bALP level and the presence of aortic calcification is present in patients with osteoporosis (10). Similarly, an in vivo study showed an increased level of circulating bALP in patients with CKD in the presence of aortic calcification (11).

In the study presented by Urena and his colleagues in 1996 (23) demonstrated that bone formation and bone resorption parameters correlated better with plasma bALP levels, rather than with ALP or iPTH levels. Accordingly, plasma bALP levels were the best predictors bind with plasma iPTH levels, the predictive value of this marker was even increased. Previous studies suggested that plasma bALP could be a sensitive marker in the assessment of bone turnover in uremic patients with secondary hyperparathyroidism. They correlated with both bone formation and resorption parameters better than iPTH and ALP did (24).

Elevated levels of bone alkaline phosphatase virtually exclude an adynamic renal bone disease (25); however, elevations of bALP along with total ALP may be seen in cases of severe osteomalacia. Combinations of biochemical markers hold promise at least for the differentiation for high-turnover versus adynamic forms (26).

It may be considered that high-turnover state of bone is driven by secondary hyperparathyroidism, which is characterized by poorly differentiated osteoblast precursors manifesting a fibroblastic phenotype and by increased osteoclastic activity. This results in net bone resorption, fibrosis of the bone marrow space and release of calcium and phosphate into the extracellular fluid (27). Both ions could function as promoters of vascular smooth-muscle cell phenotypic differentiation into osteoblast-like cells and initiate the vascular calcification process (18). Concerning the role of secondary hyperparathyroidism on vascular calcification, Neves and his colleagues in 2007(28) showed that normal and uremic rats submitted to parathyroidectomy that subsequently received PTH replacement in supraphysiological doses developed intense aortic medial calcification, with some animals showing coronary calcification. These findings suggested that high PTH levels induced high bone turnover and medial calcification independent of uremia (18).

In this study left ventricular diameters include interventricular septal thickness at end diastole (IVS), posterior wall thickness at end diastole (PWT) and left ventricular internal diameter at end diastole (EDD) and systole(ESD) were highly significant increased in patients with chronic hemodialysis than control group (P<0.001). Also left ventricular Ejection fraction (EF) was highly significant decreased in patients with chronic hemodialysis than control group. Resic and his colleague in 2009 in their study found increase in left ventricular thickness and hypertrophy in 55.8% and left ventricular dysfunction in 60% of patients with chronic hemodialysis than control group.

The present study, revealed that intima-media thickness was highly significant increased in patients with chronic hemodialysis than control group (P<0.001). Common carotid artery intima-media thickness as a measure of subclinical vascular disease was found to be increased in patients with chronic hemodialysis than control group. (30).

In this study it was found that mitral valve calcification was found in 27.4% and aortic valve calcification was found in 71.4% of hemodialyzed patients. Vascular calcification is highly correlated

with cardiovascular disease mortality, especially in patients with ESRD. In addition to the devastating effects of inappropriate biomineralization seen in cardiac valvulopathies, calciphylaxis, and idiopathic arterial calcification, valvular calcification is common in patients with end-stage renal disease, and is associated with an unfavorable prognosis. Raggi and his colleagues in 2004(31) found that mitral valve calcification was seen in 46% of subjects and aortic valve calcification in 33% in hemodialysis patients. Also valvular calcifications, predominant in aortic and mitral positions, were found in 30-50% of hemodialyzed patients (32).

Beddhu and his colleagues in 2009(7) observed that independent of liver function tests and serum calcium and phosphorus, serum alkaline phosphatase might be a risk factor for death in African-American patients in CKD stages III and IV. The potential mechanisms for this observation remain unclear. ALP has been shown in histologic sections of vessels obtained from patients with CKD-associated calcific uremic arteriopathy (33 &34), ALP seems to play a mediating and instrumental role (6). It is likely that the ALP-mortality association in CKD, including the observed link with cardiovascular death, is related to vascular calcification through its pyrophosphate link (4),

However, there is mounting evidence that alkaline phosphatase can promote vascular calcification by hydrolyzing pyrophosphate in the arterial wall (3). For instance, in calcified diabetic arteries, alkaline phosphatase is upregulated (35). In the aorta of uremic rats, the hydrolysis rate of pyrophosphate was increased compared with controls (3). This increase was reduced by levamisole, a nonspecific inhibitor of alkaline phosphatase. These experimental data suggested a role for alkaline phosphatase in the development of uremic calcification. Indeed, in a longitudinal study of 134 stage IV and V CKD patients, higher levels of serum alkaline phosphatase were associated with progressive arterial calcification (36).

The protective effects of low bALP and ALP levels include the mechanisms via pyrophosphate. Experimental data link high ALP to the development of coronary artery calcification with their ability to hydrolyze inorganic pyrophosphate (37). Pyrophosphate is a potent inhibitor of vascular calcification, and its biologic action is reduced by phosphatases. High levels of bALP were associated with mortality and specific fatal events (38). They concluded that high levels of bALP were strongly associated with short term mortality in dialysis patients, pointing out the important impact of bone turnover. Longitudinal assessments of bALP may be useful for the treatment monitoring in clinical practice in dialysis patients.

Indeed, genetic ablation of tissue-nonspecific ALP leads to amelioration of soft tissue calcification in animal studies. Some novel inhibitors of the physiologic pyrophosphatase activity of ALP are capable of reducing vascular calcification in animal models (6), however, the ALP-death link may have additional causes, such as its relationship with inflammation or malignancies (8). The current study shows that CRP and hsCRP are significantly higher in MHD group compared to the control group ($P<0.001$). In addition to vascular calcification, there are other potential mechanisms that may mediate the associations of serum alkaline phosphatase with increased mortality. One of the potential explanations is that higher serum alkaline phosphatase might be associated with inflammation. Damera *et al.*, 2011 (39) found that serum alkaline phosphatase level has been associated with elevated CRP level which is a marker of inflammation. Atherosclerosis has been well established to be an inflammatory process, (40), in another study of Chinese adults, higher serum alkaline phosphatase levels were also associated with elevated CRP levels. (41).

Several studies have documented the importance of abnormal mineral metabolism (42) and inflammation (43) as pivotal factors for the increased cardiovascular risk in CKD patients. Two previous studies in hemodialysis, with a limited number of patients, showed that a high Ca x P was associated with high CRP concentrations (44). In summary elevated serum alkaline phosphatase levels might reflect not only altered bone mineral metabolism but also an atherogenic milieu. these data may have major clinical and public health implications given the high burden of vascular calcification in patients with CKD (9). Because of the significant association of osteodystrophy with cardiovascular calcification, cardiovascular disease and death, diligent treatment of high-turnover bone disease may be an effective measure to improve survival in CKD. Close monitoring of ALP levels may be useful when considering initiation or changes of the therapy. To better understand the natural course of renal osteodystrophy and its complications in CKD; and to evaluate the effectiveness of current and future treatments including vitamin D analogs, calcimimetics and other medications such as ALP inhibitors in improving osteodystrophy and clinical outcome in CKD population.

Conclusion:

Plasma bALP should be measured with a reliable immunoassay in hemodialysis patients. It represents a highly sensitive and specific biochemical marker of skeletal remodeling in these

patients, even better when associated with plasma iPTH levels. Abnormal mineral metabolism and inflammation are pivotal factors for the increased cardiovascular risk in CKD patients.

These findings may have major clinical and public health implications given the high burden of vascular calcification in patients with CKD and potential therapeutic strategies e.g. ALP inhibitors to modulate this pathway to mitigate or prevent risk for vascular calcification and improve the poor survival of patients with CKD which can be evaluated and detected by echocardiography and carotid Duplex .

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References:

1-Shanahan CM (2005). Mechanisms of vascular calcification in renal disease. Clin. Nephrol. 63:146-157.
2- Lomashvili KA; Cobbs S; Hennigar RA; (2004). Phosphate-induced vascular calcification: Role of pyrophosphate and osteopontin. J. Am. Soc. Nephrol. 15:1392-1401.
3- Lomashvili KA; Garg P; Narisawa S (2008). Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: Potential mechanism for uremic vascular calcification Kid. Int. 73:1024-1030.
4-Schoppet M and Shanahan CM (2008). Role for alkaline phosphatase as an inducer of vascular calcification in renal failure? Kid. Int. 73:989-991.
5- Kalantar-Zadeh K; Kuwae N; Regidor DL., (2006). Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kid. Int. 70:771-780.
6-Narisawa S; Harmey D; Yadav MC., (2007). Novel inhibitors of alkaline phosphatase suppress vascular smooth muscle cell calcification. J. Bone Miner. Res. 22:1700-1710.
7-Beddhu S; Ma X; Baird B., (2009). Serum Alkaline Phosphatase and Mortality in African Americans with Chronic Kidney Disease. Clin. J. Am. Soc. Nephrol. 4:1805-1810.
8-Regidor DL; Kovesdy CP; Mehrotra R., (2008). Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. J. Am. Soc. Nephrol. 19:2193-2203.
9-Shantouf R; Kovesdy CP; Kim Y., (2009). Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients.Clin. J. Am. Soc. Nephrol. 4:1106-1114.
10-Iba K; Takada J and Yamashita T (2004). The serum level of bone-specific alkaline phosphatase activity is associated with aortic calcification in osteoprosis patients. J. Bone Miner. Metab. 22:594-596.
11-Avbersek-Luznik I; Balon BP; Rus I;., (2005). Increased bone resorption in HD patients: is it caused by elevated RANKL synthesis? Nephrol. Dial. Transplant. 20:566-570.
12-Ross R (1999). Atherosclerosis: an inflammatory disease. N. Engl. J. Med. 340:115-126.
13--Ridker PM; Hennekens CH; Buring JE., (2000). C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N. Engl. J. Med. 342:836-843.
14-Ridker PM (2001). High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 103:1813-1818.
15-Mendall MA; Strachan DP; Butland BK., (2000). C-reactive protein relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. Eur. Heart J. 21:1584-1590.
16--Pasceri V; Willerson JT and Yeh ET (2000). Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 102:2165-2168.
17-Kovesdy CP; Ahmadzadeh S; Anderson JE (2008). Secondary hyperparathyroidism is associated with higher mortality in men with moderate to severe chronic kidney disease. Kid. Int. 73:1296-1302.
18-Barreto DV; Barreto FC; de Carvalho AB (2008). Association of changes in bone remodeling and coronary calcification in hemodialysis patients: A prospective study. Am. J. Kid. Dis. 52(6): 1139-1150.
19-Magnusson P; Sharp CA; Magnusson M., (2001). Effect of chronic renal failure on bone turnover and bone alkaline phosphatase isoforms. Kid. Int. 60:257-265.
20-Uhlig K; Bems JS; Kestenbaum B., (2010). KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guidelinefor the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis 55(5):773-799.
21-Palmer SC; McGregor DO; Macaskill P., (2007). Meta-analysis: Vitamin D compounds in chronic kidney disease. Ann. Intern. Med. 147:840-853.
22-Kovesdy CP and Kalantar-Zadeh K (2008). Bone and mineral disorders in predialysis CKD. Int. Urol. Nephrol. 40:427-440.
23-Urena P; Hruby M; Ferreira A; Ang KS., (1996). Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. J. Am. Soc. Nephrol. 7:506-512.
24-Garnero P and Delmas PD (1993). Assessment of

the serum levels of bone alkaline phosphatase with a new immunoradiometric assay in patients with metabolic bone disease.J. Clin. Endocrinol. and Metab. 77:1046-1053.
25-Schwarz C; Sulzbacher I and Oberbauer R (2006). Diagnosis of renal osteodystrophy. Eur. J. Clin. Invest. 36(s2):13-22.
26-Brandenburg VM and Floege J (2008). Adynamic bone disease—bone and beyond. Oxford Journals,Medicine,NDT Plus 1(3):135-147.
27-Gonzalez EA; Lund RJ; Martin KJ;., (2002). Treatment of a murine model of high-turnover renal osteodystrophy by exogenous BMP-7. Kid. Int. 61:1322-1331.
28-Neves KR; Graciolli FG; dos Reis LM (2007). Vascular calcification: Contribution of parathyroid hormone in renal failure. Kid.Int. 71:1262-1270.
29-Resic H; Ajanovic S; Kukavica N (2009). Plasma levels of brain natriuretic peptides and cardiac troponin in hemodialysis patients. Bosn J. Basic Med Sci. 9(2):137-141.
30-Rampersaud E; Bielak LF; Persa., (2008). The association of coronary artery calcification and carotid artery intima-media thickness with distinct, traditional coronary artery disease risk factors in asymptomatic adults. Am. J. of Epidemiology 168(9):1016-1023.
31-Raggi P; Bommer J and Chertow GM (2004). Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer.J. Am. Soc. Nephrol. 15:2959-2964.
32-Stompor T; Raizer M; Pasowicz M (2006). Coronary artery calcification, common carotid artery intima-media thickness and aortic pulse wave velocity in patients on peritoneal dialysis. Int. J. Artif Organs 29(8):736-744.
33-Reslerova M and Moe SM (2003). Vascular calcification in dialysis patients: Pathogenesis and consequences. Am. J. Kid. Dis. 41:S96-S99.
34-Schoppet M; Shroff RC; Hofbauer LC., (2008). Exploring the biology of vascular calcification in chronic kidney disease: What's circulating ? Kid. Int. 73:384-390.
35-Fadini GP; Pauletto P; Avogaro A (2007). The good and the bad in the link between insulin resistance and vascular calcification. Atherosclerosis 193:241-244.
36-Sigrist MK; Taal MW; Bungay P (2007). Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. Clin. J. Am. Soc. Nephrol. 2:1241-1248.
37-Towler DA, (2005). Inorganic pyrophosphate: A paracrine regulator of vascular calcification and smooth muscle phenotype. Arterioscler. Thromb. Vasc. Biol. 25:651-654.
38-Drechsler Ch,Verduijn M, Pilz S, Krediet RT, Dekker FW, Wanner Ch, Ketteler M, Boeschoten EW, and Brandenburg V (2011). Bone alkaline phosphatase and mortality in dialysis patients. Clin. J. Am. Soc. Nephrol. as doi:10.2215/CJN.10091110.
39-Damera S; Raphael KL; Baird BC., (2011). Serum alkaline phosphatase levels associate with elevated serum C-reactive protein in chronic kidney disease.Kidney International 79, 228-233.
40-Kerner A; Avizohar O; Sella R., (2005). Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. Arterioscler. Thromb. Vasc. Biol. 25:193-197.
41-Cheung BM; Ong KL; Cheung RV.: (2008). Association between plasma alkaline phosphatase and C-reactive protein in Hong Kong Chinese. Clin. Chem. Lab. Med. 46:523-527.
42-Young EW; Albert JM; Satayathum S:, (2005). Predictors and consequences of altered mineral metabolism: The dialysis Outcomes and Practice Patterns Study. Kid. Int. 67:1179-1187.
43-Parekh RS; Plantinga LC; Kao WH, (2008). The association of sudden cardiac death with inflammation and other traditional risk factors. Kid. Int. 74:1335-1342.
44-Nasri H (2006). Linkage of elevated Ca x P product with inflammation in maintenance hemodialysis patients. Minerva Urol. Nephrol. 58:339-345.

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