

# ASSOCIATION OF SERUM ALKALINE PHOSPHATASE AND CORONARY ARTERY CALCIFICATION IN HEMODIALYSIS PATIENTS

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## Introduction

- Cardiovascular mortality among the End Stage Renal disease population is as high as 10- to 30- fold that of the general population despite age, race, gender, and presence of diabetes
- Coronary artery calcification (CAC) is associated with cardiovascular morbidity & mortality in hemodialysis patients
- Several mechanisms have been implicated for the high prevalence of vascular calcification in CKD including diabetes mellitus, hypertension, dyslipidemia, bone and mineral disorders, secondary hyperparathyroidism (SHPT), chronic inflammation, and deficiency of anti-calcemic factors such as fetuin.
- High serum levels of alkaline phosphatase are associated with increased death risk in epidemiologic studies of maintenance hemodialysis (MHD) patients.
- Recent in vitro studies have shown a link between alkaline phosphatase and vascular calcification in chronic kidney disease via the pyrophosphate pathway
- We hypothesized that CAC is independently associated with increased serum alkaline phosphatase levels in MHD patients.

## Methods

- We studied a randomly selected group of MHD patients who participated in the substudy of the *Nutritional and Inflammatory Evaluation in Dialysis* (NIED) Study
- Of the 893 MHD patients in the original cohort, 176 of these individuals were randomly invited to undergo additional tests as parts of the NIED Substudy
- Of the Substudy, 153 patients had both coronary artery calcification assessment by electron beam tomography and alkaline phosphatase (AlkPhos) measured
- CAC>0 were present in 137 (of the 153) subjects
- Demographics, nutritional measures, hemodialysis treatment measures, biochemical markers, and medications were assessed in the subject pool
- We dichotomized AlkPhos at 120 IU/L as recently suggested in an epidemiologic study as the cutoff value above which death risk is increased, looking at mean total CACS and within different coronary arteries, both for number of calcified lesions and for artery-specific CACS
- We examined the odds of having a CACS ≥400 using continuous cubic splines analyses to explore the non-linear association between CACS and AlkPhos
- Multivariate logistic regression models were fitted to construct odds ratio (OR) of CACS ≥400 in the 1<sup>st</sup> and 3<sup>rd</sup> tertiles of serum AlkPhos before and after controlling for confounding covariates using the middle tertile as the reference

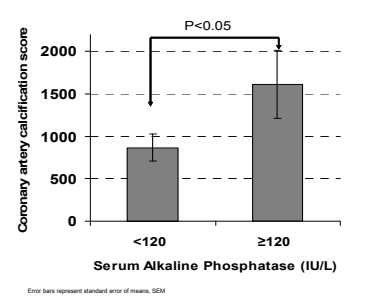
Baseline Characteristics of 137 MHD patients with CACS >0 according to tertiles of CACS

Variable	coronary artery calcification score			P trend
	1 <sup>st</sup> tertile (n=45)	2 <sup>nd</sup> tertile (n=45)	3 <sup>rd</sup> tertile (n=47)	
<b>Demographic</b>				
Age (years)	46±14	60±10	60±11	<0.001
Women (%)	49	24	38	0.3
Race: % African-American	51	40	47	0.7
Ethnicity: % Hispanic	36	40	26	0.3
Diabetes mellitus (%)	36	64	81	<0.001
<b>Nutritional Measures</b>				
Total protein (g/dl)	71.6±35.1	68.4±23.4	65.2±28.3	0.3
Total Cholesterol (mg/dl)	1767±745	1670±540	1639±681	0.4
Body mass index (kg/m <sup>2</sup> )	26.5±8.5	25.8±4.4	27.7±5.2	0.4
Triceps skinfold (mm)	17.3±10.1	15.1±9.0	16.9±9.2	0.8
Biceps skinfold (mm)	10.7±8.5	8.8±6.1	10.0±8.8	0.7
Near infrared measured body fat (%)	25.2±12.9	25.0±8.3	28.1±9.7	0.18
<b>Hemodialysis treatment measures</b>				
Dialysis vintage <6 months (%)	7	12	5	0.6
Dialysis vintage (months)	38.0±35.3	37.8±29.7	51.6±35.3	0.01
Dialysis dose (Kt/V single pool)	1.68±0.22	1.71±0.30	1.72±0.28	0.4
βPNA or nPCR (g.kg <sup>-1</sup> .day <sup>-1</sup> )	1.06±0.19	1.06±0.24	1.12±0.27	0.23
Systolic blood pressure (mm-Hg)	146±28	156±23	157±26	0.06
Diastolic blood pressure (mm-Hg)	79±17	78±15	77±16	0.5
<b>Biochemical measurements</b>				
Serum albumin (g/dl)	4.03±0.28	3.96±0.28	3.98±0.28	0.4
transferrin (prealbumin) (mg/dl)	31.9±9.7	28.7±8.5	30.1±8.3	0.4
triglycerides (mg/dl)	138±68	144±100	164±165	0.3
total cholesterol (mg/dl)	156±43	151±37	158±43	0.22
low density lipoprotein-C (mg/dl)	92±37	83±25	79±31	0.06
high density lipoprotein-C (mg/dl)	37±9	39±14	34±16	0.3
creatinine (mg/dl)	11.4±3.3	10.2±2.9	10.5±2.9	0.20
ferritin (ng/ml)	568±406	625±475	744±406	0.05
iron saturation ratio (%)	36.1±11.0	35.8±12.1	34.1±10.0	0.4
calcium (mg/dl)	9.8±0.7	9.4±0.6	9.8±0.5	0.6
phosphorus (mg/dl)	5.7±1.2	5.6±1.3	5.5±1.2	0.5
calcium X phosphorus product (mg <sup>2</sup> /dl <sup>2</sup> )	55.7±12.5	52.7±11.5	53.2±11.5	0.3
intact PTH (pg/ml)	349±377	256±188	242±169	0.053
alkaline phosphatase (IU/L)	104±51	120±59	126±56	0.08
alkaline phosphatase ≥120 (IU/L) %	23	33	45	0.03
serum AST (SGOT) (U/L)	17.9±11.2	20.3±18.5	18.4±7.7	0.9
bicarbonate (mg/dl)	22.3±2.8	22.4±3.0	22.6±3.1	0.6
total homocysteine (μmol/l)	26.0±8.3	26.0±9.8	27.5±8.3	0.6
C-reactive protein (mg/l)	5.5±6.5	4.7±4.8	4.5±4.4	0.9
interleukin-6 (pg/ml)	22.4±9.5	7.9±5.4	11.0±8.4	0.04
Tumor necrosis factor-α (pg/ml)	6.2±2.9	5.8±2.8	6.4±2.7	0.4
Blood hemoglobin (g/dl)	12.2±0.7	12.5±0.7	12.1±0.7	0.3
WBC (×1000 cell/μl)	6.6±2.1	7.0±1.6	6.8±1.5	0.6
lymphocyte (% of total WBC)	28.3±8.4	23.5±6.1	22.5±7.8	<0.001
<b>Medications</b>				
Erythropoietin dose (1,000 U/week)	11.4±2.0	10.0±1.2	13.6±1.1	0.3
Paricalcitol dose (mg/month)	69±83	41±25	49±53	0.17

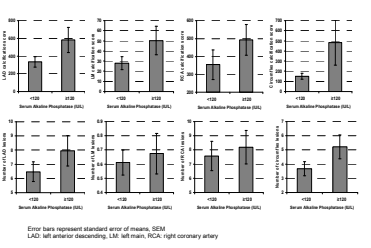
\* Kt/V, dialysis dose; βPNA, normalized protein catabolic rate; SGOT, serum glutamic oxaloacetic transaminase (Aspartate aminotransferase); CRP, C-reactive protein; WBC, white blood cell count.

## Results

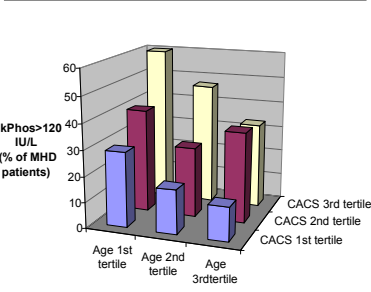
Mean Total CACS in MHD patients with Serum AlkPhos less and more than 120 IU/L



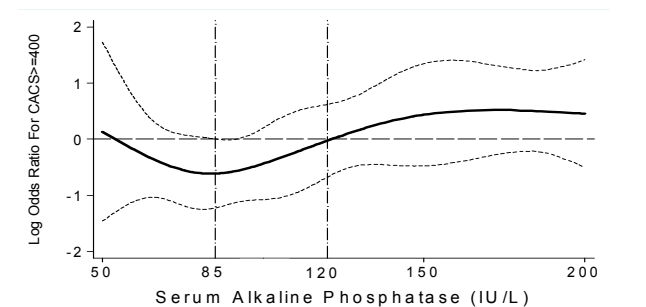
CACS and frequency of calcified lesions in the four coronary arteries in MHD patients with serum AlkPhos less and more than 120 IU/L



Proportion of MHD patients with an AlkPhos ≥120 IU/L in tertiles of age and CACS



Log odds ratio of having CACS ≥400 across spectrum of serum AlkPhos in 137 MHD patients



Unadjusted and adjusted O.R. of CACS ≥400 across tertiles of serum AlkPhos

	Serum alkaline phosphatase (IU/L)			
	First tertile <85 (n=45)	P	Second tertile 85 to 119 (n=46)	Third tertile ≥120 (n=46)
Unadjusted odds ratios	1.96 (0.84-4.55)	0.12	1.00 (reference)	3.52 (1.49-8.29)
Adjusted odds ratios				
Age	2.22 (0.89-5.54)	0.09	1.0 (reference)	4.63 (1.79-11.98)
age + sex	2.27 (0.90-5.74)	0.08	1.0 (reference)	5.98 (2.16-16.58)
age + sex + DM	2.43 (0.93-6.37)	0.07	1.0 (reference)	6.21 (2.17-17.76)
age + sex + DM + Charlson	2.89 (1.05-7.96)	0.04	1.0 (reference)	6.03 (2.09-17.39)
age + sex + DM + Charlson + Vintage	3.01 (1.01-8.99)	0.05	1.0 (reference)	5.75 (1.84-18.02)
age + sex + DM + Charlson + Vintage + IL-6 + SCOT	2.41 (0.79-7.39)	0.12	1.0 (reference)	5.03 (1.55-16.34)

DM, diabetes mellitus; Charlson, modified Charlson comorbidity score; IL-6, interleukin-6; SCOT, serum glutamic oxaloacetic transaminase (aspartate aminotransferase). Log transformed value of dialysis vintage, IL-6, and SCOT were used in these analyses.

## Conclusion

Serum AlkPhos, mainly levels greater than 120 mg/dl, may be a predictor of coronary calcification in MHD pts, independent of case-mix and inflammation.

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