

Original Paper

Serum Alkaline Phosphatase Levels and Left Ventricular Diastolic Dysfunction in Patients with Advanced Chronic Kidney Disease

Olimpia Ortega Isabel Rodriguez Julie Hinostroza
Nuria Laso Ramiro Callejas Paloma Gallar Carmen Mon
Juan Carlos Herrero Milagros Ortiz Aniana Oliet Ana Vigil

Nephrology Service, Hospital Severo Ochoa, Leganes, Spain

Key Words

Alkaline phosphatase · Left-ventricular dysfunction · Liver congestion · Chronic kidney disease · Hypervolemia

Abstract

Background: High levels of alkaline phosphatase (ALP) have been associated with increased mortality in patients with advanced chronic kidney disease (CKD). We hypothesize that elevated ALP could be partly explained by subclinical liver congestion related to left ventricular diastolic dysfunction. **Methods:** Doppler echocardiography was performed in 68 patients with advanced CKD followed up for a median of 2.1 years. Time-averaged levels of ALP and γ -glutamyl transferase (GGT) were compared between patients with and without diastolic dysfunction. We also evaluated the effect of intensifying diuretic treatment on ALP levels in a small group of 16 patients with high ALP and signs of volume overload. **Results:** ALP correlated significantly ($p < 0.001$) with GGT but not with parathyroid hormone ($p = 0.09$). Patients with diastolic dysfunction showed higher ALP ($p = 0.01$), higher GGT ($p = 0.03$) and lower albumin ($p = 0.04$). The highest values of ALP were observed in patients with diastolic dysfunction plus pulmonary hypertension ($p = 0.01$). Intensifying diuretic therapy in a subgroup of patients with signs of fluid overload induced a significant reduction in body weight, GGT ($p < 0.001$) and ALP

levels ($p < 0.001$). **Conclusions:** Elevated ALP in patients with advanced CKD could be partly explained by subclinical liver congestion related to left ventricular diastolic dysfunction, hypervolemia or both. The worse prognosis of these patients could be explained by their myocardial damage.

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Introduction

Left ventricular (LV) diastolic dysfunction, related to LV hypertrophy and myocardial fibrosis, is highly prevalent among patients with chronic kidney disease (CKD) [1, 2] and its prevalence and severity increases in parallel with the severity of CKD [3, 4].

The pathophysiology of diastolic dysfunction includes delayed relaxation resulting in an upward displacement of the diastolic pressure-volume relationship. In patients with diastolic dysfunction, a small increase in end-diastolic volume may lead to an exaggerated increase in end-diastolic pressure, leading to an increase in left atrial and pulmonary capillary wedge pressure, causing pulmonary hypertension and symptoms of pulmonary congestion [5]. Finally, pulmonary hypertension can induce right-side heart failure and liver congestion. Several authors [6–8] have observed that the liver function test profile typical of heart failure is a predominantly cholestatic profile with normal transaminase levels but with increased bilirubin, γ -glutamyl transferase (GGT) and alkaline phosphatase (ALP).

High levels of ALP have been associated with increased mortality in hemodialysis [9, 10] and pre-dialysis [11] patients, suggesting that this association could be part of the novel association between mineral and bone disease and mortality among patients with CKD [12, 13]. The authors highlighted that this association was independent of liver disease. However, as marker of liver disease only hepatitis C virus serology and transaminase levels were measured whereas cholestatic profile was not analyzed.

We hypothesize that elevated ALP levels in patients with CKD could be partly explained by subclinical liver congestion related to LV diastolic dysfunction, hypervolemia or both conditions which finally can induce pulmonary hypertension and subclinical right-side heart failure.

Patients and Methods

Sixty eight patients with CKD stages IV and V, followed in our single outpatient pre-dialysis unit, were enrolled. Clearance of creatinine (CrCl) was measured using the 24-hour urine collection method.

Demographic characteristics at the entry of the initial evaluation were recorded. Characteristically, the patients enrolled in this study had low comorbidity as those patients with CKD and associated cardiopathy (ischemic or valvular cardiopathy) are usually followed in our special cardio-renal unit. Patients were followed up for a median of 2 years. Follow-up clinical and laboratory data recorded during follow-up in relation to outpatient visits were also extracted and utilized in time-varying analysis.

Two-dimensional echocardiography was performed. LV diastolic function was assessed using mitral valve inflow Doppler. LV filling pressure was assessed using the ratio of the peak early mitral inflow velocity (E) to medial mitral annular early diastolic velocity E' . LV filling pressure was considered to be elevated when $E/E' > 10$. Pulmonary hypertension was calculated in those patients with tricuspid regurgitation using the Bernoulli equation [14], measuring the pressure gradient between right ventricle and right atrium.

Pulmonary hypertension was considered when pulmonary artery systolic pressure was higher than 30 mm Hg. Patients were evaluated monthly or every other month during a median follow-up period of 2.2 years. In each visit, patients were weighed and blood pressure (BP) was measured using a standard mercury sphygmomanometer. Before each visit, blood samples were obtained from patients after overnight fasting. Blood hemoglobin (Hb), serum albumin, cholesterol, parathyroid hormone (PTH) and cholestatic profile markers (ALP and GGT) were measured by routine laboratory methods. A high-sensitivity assay for C-reactive protein (CRP) measurement was used. Serum CRP was measured by nephelometry on a BNA II (Dade Behring, Liederbach, Germany). N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was determined using chemiluminiscent Elecsys proBNP sandwich immunoassay (ECLIA) on an Elecsys 2010 (Roche Diagnostic, Mannheim, Germany). The levels of 25-OH vitamin D were determined by radioimmunoassay (Dia Sorin, Stillwater, Minn., USA). The treatment with vitamin D supplements was also recorded.

Time-averaged clinical and laboratory data were compared between patients with and without elevated LV filling pressure and also between patients with and without pulmonary hypertension.

In a second part of the study, we analyzed the possible effect on ALP levels of intensifying diuretic treatment in a group of patients with high levels of ALP and signs of overhydration, even when these signs of overhydration were subclinical. Those patients who experienced an increase in body weight in parallel with an increase in blood pressure values compared to previous visits were considered as possibly overhydrated. We analyzed the possible variation in ALP levels in these patients after intensifying diuretic treatment. The analysis was made only in those patients who experienced a reduction in body weight and blood pressure in the subsequent visit. Finally, the analysis was made in a small subgroup of 16 patients.

Continuous data are expressed as mean \pm SD or median (interquartile range), depending on their distribution. Unpaired or paired t test was used for comparison of normally distributed variables. For variables with skewed distribution, the χ^2 test of the Fisher exact test was used. Correlation between continuous variables was assessed using the Pearson or Spearman correlation coefficient. A two-tailed p value <0.05 was considered statistically significant. Data were performed using SPSS (version 12.0).

Results

Demographic characteristics are expressed in table 1. As the patients were relatively old, vascular and diabetic nephropathy were the most frequent causes of CKD.

Elevated LV filling pressure was observed in 49 (76%) of the patients. However, only 6 patients (13%) showed echocardiographic data of pulmonary hypertension in addition to an increased LV filling pressure.

Forty-six patients (74%) received supplements of vitamin D and in 15 patients an arteriovenous fistula was created during the follow-up.

Time-averaged systolic BP levels and time-averaged levels of all the laboratory parameters measured during the study period are expressed in table 2. Time-averaged ALP correlated significantly with GGT ($r = 0.5$; $p < 0.001$) and inversely with serum albumin ($r = -0.28$; $p = 0.04$). The correlation between ALP and GGT is expressed in figure 1. No significant correlation between ALP and PTH ($p = 0.09$) was found. ALP did not correlate significantly either with plasma levels of 25-OH vitamin D ($p = 0.59$) or systolic BP ($p = 0.24$), blood Hb ($p = 0.14$), CRP ($p = 0.09$), patient age ($p = 0.23$) or CrCl at baseline.

Table 1. Demographic characteristics of the patients enrolled in the study

Number	68
Age, years	63 ± 13
Sex (men)	44 (69)
Basal CrCl, ml/min	23 ± 6
Causes of CKD	
Vascular	20 (31)
Diabetes	19 (30)
Chronic GN	10 (16)
Interstitial	8 (12)
PCKD	3 (5)
Unknown	3 (5)
Others	1 (2)
Diastolic dysfunction	49 (76)
Pulmonary hypertension	6 (13)
Vitamin D supplements	46 (74)
Vascular access	15 (24)
Follow-up, years	2.1 (1.2–2.3)

Data expressed as number (percentage), mean ± SD or median (interquartile range). CrCl = Clearance of creatinine; CKD = chronic kidney disease; GN = glomerulonephritis; PCKD = polycystic kidney disease.

Table 2. Mean time-averaged values of systolic blood pressure (BP) and all the laboratory data measured during the study period

Systolic BP, mm Hg	139 ± 11
ALP, U/l	86 ± 31
GGT, U/l	37 ± 29
PTH, pg/ml	291 ± 184
	244 (187–325)
Albumin, g/dl	4.0 ± 0.3
Cholesterol, mg/dl	186 ± 32
Hemoglobin, g/dl	12.6 ± 0.6
C-reactive protein, mg/l	4 (2–8)
NT-proBNP, pg/ml	1,339 ± 1,263

Data expressed as mean ± SD or median (interquartile range). ALP = Alkaline phosphatase; GGT = γ -glutamyl transferase; PTH = parathyroid hormone.

ALP was higher in diabetic patients (97 ± 42 U/l vs. 81 ± 24 U/l in nondiabetic patients; $p = 0.04$), whereas no significant differences between genders ($p = 0.1$) was found. Time-averaged ALP was not different ($p = 0.49$) between patients with or without an arteriovenous fistula.

The differences in clinical and laboratory data between patients with and without an increased LV filling pressure are expressed in table 3. Patients with increased LV filling pressure were older, showed higher levels of ALP and GGT and lower levels of serum albumin. Blood hemoglobin was lower in these patients although the difference did not reach statistical significance ($p = 0.09$). NT-proBNP was slightly higher, although the difference was also not significant ($p = 0.6$).

The highest values of ALP were observed in those patients who showed pulmonary hypertension in addition to an increased LV filling pressure. These patients also showed higher values of GGT and NT-proBNP. These results are expressed in table 4.

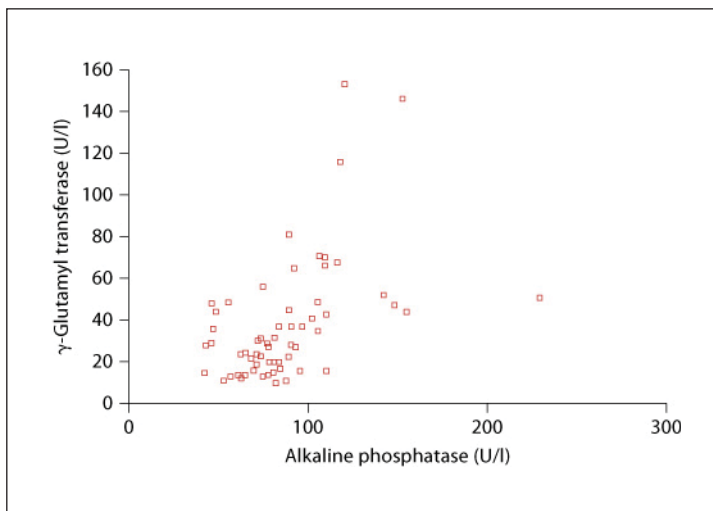


Fig. 1. A significant correlation exists between γ -glutamyl transferase and alkaline phosphatase ($r = 0.5$; $p < 0.001$).

Table 3. Comparison of demographic and time-averaged laboratory parameters between patients with high or normal left ventricular filling pressure (LVFP)

	High LVFP (n = 46)	Normal LVFP (n = 22)	p value
Age, years	67 ± 15	64 ± 11	0.02
ALP, U/l	91 ± 32	67 ± 15	0.01
GGT, U/l	41 ± 28	22 ± 9	0.03
Albumin, g/dl	4.0 ± 0.2	4.1 ± 0.2	0.04
PTH, pg/ml	295 ± 209	302 ± 164	0.9
25-OH vitamin D, ng/ml	20 ± 10	22 ± 10	0.5
Cholesterol, mg/dl	190 ± 33	171 ± 21	0.2
Hemoglobin, g/dl	12.5 ± 0.5	12.8 ± 0.6	0.09
C-reactive protein, mg/l	6.6 ± 4.9	4.8 ± 3.1	0.8
NT-proBNP, pg/ml	1,511 ± 1,472	1,206 ± 1,007	0.6

Data expressed as mean ± SD. ALP = Alkaline phosphatase; GGT = γ -glutamyl transferase; PTH = parathyroid hormone.

Table 4. Comparison of time-averaged levels of ALP, GGT and NT-proBNP between patients with and without pulmonary hypertension (PH)

	PH (n = 6)	No PH (n = 62)	p value
ALP, U/l	103 ± 27	81 ± 30	0.04
GGT, U/l	65 ± 47	30 ± 16	0.001
NT-proBNP, pg/ml	3,056 ± 1,473	937 ± 915	0.005

Data expressed as mean ± SD. ALP = Alkaline phosphatase; GGT = γ -glutamyl transferase; PTH = parathyroid hormone.

Fig. 2. Variation of γ -glutamyl transferase levels after intensifying diuretic therapy and achieving a mean body weight reduction of 1.8 ± 0.9 kg (range: 0.5–3.5 kg) in the subgroup of patients ($n = 16$) with higher levels of alkaline phosphatase ($p < 0.001$).

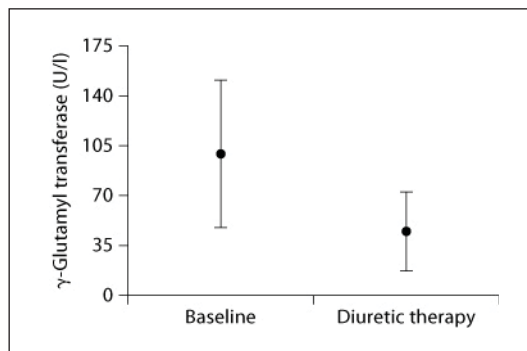
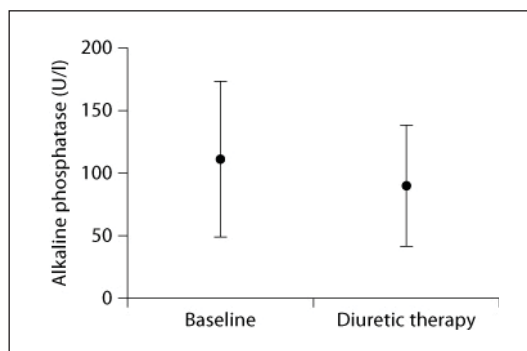


Fig. 3. Variation of alkaline phosphatase levels after intensifying diuretic therapy and achieving a mean body weight reduction of 1.8 ± 0.9 kg (range: 0.5–3.5 kg) in the subgroup of patients ($n = 16$) with higher levels of alkaline phosphatase ($p < 0.001$).



Intensifying diuretic therapy in the subgroup of 16 patients with high levels of ALP and signs of fluid overload, even subclinical, induced a significant decrease in body weight of 1.8 ± 0.9 kg (78 ± 15 kg at baseline vs. 76 ± 15 kg after intensifying diuretic therapy; $p < 0.001$) as well as in systolic BP (from 146 ± 18 mm Hg to 133 ± 16 mm Hg; $p < 0.001$) in the subsequent visit. GGT levels also decreased significantly (from 100 ± 52 U/l to 45 ± 29 U/l; $p < 0.001$) as did ALP (from 112 ± 49 U/l to 90 ± 40 U/l; $p < 0.001$). The variation in GGT and ALP levels after intensifying diuretic treatment is expressed in figures 2 and 3, respectively.

Discussion

The main findings of our study are that ALP and GGT levels were higher in CKD patients with an increased LV filling pressure and especially in those patients who in addition showed evidence of pulmonary hypertension. Time-averaged ALP and GGT levels correlated strongly with each other in our study.

Volume overload control could reduce both ALP and GGT levels probably by reducing LV volume and, therefore, LV pressure in these patients with diastolic dysfunction. Thus, our results suggest that high ALP levels among patients with advanced renal failure could be part of the cholestatic profile related to subclinical liver congestion in patients with an increased LV filling pressure, in whom a small increment in LV volume can induce an exaggerated increase in LV pressure which finally can induce pulmonary hypertension and right-side heart failure. The worse prognosis of CKD patients with high levels of ALP could therefore be explained by their myocardial damage.

The prevalence of LV hypertrophy in CKD patients is high, ranging from 34% to 78% in the different studies, with increased prevalence with declining renal function [15, 16]. Myocardial fibrosis is also highly prevalent among patients with CKD [17] and it is determinant of diastolic dysfunction, which is the most frequent echocardiographic finding among patients with advanced renal failure [4] and occurs at the very early stages of CKD [18].

When diastolic dysfunction is present, a small increment in end-diastolic volume can induce an exaggerated increase in end-diastolic pressure related to the reduced LV distensibility. This increase in LV filling pressure can induce elevated left atrial pressure with resultant pulmonary congestion, elevated right atrial pressure and finally, systemic congestion [4]. In this setting, liver congestion can occur with biochemical cholestatic profile and serum elevation of GGT and ALP.

ALP is a hydrolase enzyme responsible for removing phosphate groups for many types of molecules. Elevated serum ALP levels are often observed in renal osteodystrophy, especially in high-turnover bone disease. Several authors [9–11] have observed that high levels of ALP predict mortality among patients with CKD, supporting the novel association between mineral and bone disease and mortality among patients with CKD. Although patients with higher levels of ALP showed higher levels of PTH, the authors highlight that high levels of ALP predict mortality after adjustment of calcium, phosphate and PTH. Furthermore, the death risk associated with higher ALP was increasing linearly, in opposition to an U-shaped relationship found between PTH and mortality.

There is mounting evidence that alkaline phosphatase can promote vascular calcification by hydrolyzing pyrophosphate in the arterial wall [19]. Thus, the authors suggest progressive vascular calcification as a possible underlying mechanism explaining the association between ALP levels and mortality.

However, serum ALP may also increase as a result of liver disorders. In the previous studies [9–11], the mortality risk of high ALP levels was maintained independent of liver disease. However, as marker of liver disease only transaminases and serological markers were analyzed, whereas cholestatic profile was not measured. In another study performed in patients with reduced GFR between 20 and 65 ml/min, Beddhu and colleagues [20] determined not only transaminase levels but also bilirubin and GGT levels in their patients. They observed no significant differences across the alkaline phosphatase group regarding serum calcium and phosphorus as well as serum aspartate aminotransferase, alanine aminotransferase and bilirubin. However, the high alkaline phosphatase group had higher GGT levels. In this study, after adjusting for liver function tests, high serum alkaline phosphatase was not associated with increased mortality in the first 2 years of follow-up, but was associated with increased mortality after 2 years of follow-up.

In the present study, we found a strong correlation between time-averaged ALP and GGT in our patients. On the contrary, no significant association between ALP and PTH was found. This is not a surprising finding as most of our patients received vitamin D supplements, and a recent meta-analysis showed that the treatment of renal osteodystrophy by means of vitamin D analogs can effectively decrease ALP levels, even though such a treatment may not decrease PTH consistently [21]. Thus, it seems that high ALP levels are mainly related to liver disorders in these patients in whom renal osteodystrophy is treated. As both ALP and GGT were higher in patients with increased LV filling pressure and especially in those patients with pulmonary hypertension, we could hypothesize that subclinical liver congestion could explain the biochemical cholestatic profile. Furthermore, the control of volume overload by intensifying diuretic therapy could reduce ALP and GGT levels in our patients, probably by reducing LV volume and pressure.

Serum alkaline phosphatase has been associated with elevated CRP levels [22] and high levels of CRP have been also associated with an increased LV filling pressure among patients

with CKD [23–25]. This association supports our hypothesis that high ALP levels are mainly of liver origin among patients with CKD. In patients with diastolic dysfunction, overhydration increases LV pressure, finally leading to an increased right-side pressure and hepatic congestion. Right-side heart failure can also induce systemic inflammation. The hypothesis supporting this association between heart failure and inflammation has been proposed several years ago. Niebauer et al. [26] suggested that during acute cardiac decompensation, acute venous mesenteric venous congestion with subsequent altered gut permeability for endotoxins would lead to translocation of these materials into the circulation, inducing the inflammatory response. However, in our study, CRP was higher, although not significant, in those patients with increased LV filling pressure, although no patients showed evident clinical signs of heart failure. There was a trend to correlation between ALP and CRP in our patients, although it did not reach statistical significance.

The major limitation of our study is that it is a small study including a small number of patients with advanced CKD followed at a single center. Another limitation is that serum calcium and phosphorus levels were not recorded. However, this limitation does not invalidate our results suggesting that liver disease, probably liver congestion, could be the main source of serum ALP among patients with advanced renal failure.

In summary, in the present study we found a strong correlation between ALP and GGT levels among patients with advanced CKD, whereas the correlation with PTH was not significant. Both parameters, ALP and GGT, were higher in those patients with increased LV filling pressure and, especially in patients with pulmonary hypertension, suggesting that liver congestion and not mineral and bone disease could be the main source of high levels of ALP in these patients. Furthermore, control of volume overload could reduce ALP and GGT probably by reducing LV volume and, therefore, LV pressure. Thus, our results suggest that the worse prognosis of CKD patients with high levels of ALP could be related to their myocardial damage. Further studies are required in order to analyze whether reduction of ALP by a strategy of strict volume control could improve the prognosis of CKD patients with high levels of alkaline phosphatase.

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