Left ventricular hypertrophy in patients with chronic kidney disease under conservative treatment

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Abstract

Cardiovascular disease (CVD) remains the major cause of death in patients with chronic kidney disease (CKD). Left ventricular hypertrophy (LVH) is present in 75% of patients starting dialysis, suggesting that LVH might be present from an early stage of CKD. Few studies have addressed the predialysis prevalence of LVH. This study evaluated 309 clinically stable patients under treatment for at least three months at five Brazilian centers. Biochemical profile and inflammatory markers were assessed. Data were shown as mean ± SD. Left ventricular hypertrophy was present in 53% of the patients, whose mean age was 60 ± 13years. The mean age of those without LVH was 55 ± 14 years. Diabetes mellitus was the underlying disease in 35% of the patients in both groups. Estimated glomerular filtration rate was 30 ± 11 and 32 ± 12 mL/min for patients with and without LVH, respectively ($p = 0.19$). The distribution of patients showed that 60% of those with LVH were in stage 4. Multivariate logistic regression analysis indicated the following independent determinants for LVH: age ($p < 0.001$); calcium ($p < 0.001$); hemoglobin ($p < 0.048$); and diastolic blood pressure ($p < 0.001$). Systolic blood pressure, lipids, and inflammatory markers showed no correlation with LVH. In conclusion, the incidence of LVH was high even among patients under conservative treatment, and, except for age, LVH correlated with reversible factors. The need for strictly diagnosing CKD and preventing LVH in the predialysis phase is emphasized to decrease mortality due to CVD in that population.

Keywords: chronic kidney failure, left ventricular hypertrophy, therapy.

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Introduction

Cardiovascular disease (CVD) is still the major cause of death in patients with end-stage chronic kidney disease (ES-CKD)[1], with a mortality rate approximately 10 to 30 times greater than that of the general population.[2] Heart disease or heart failure are causes of morbidity and mortality in that population, and advanced cardiomyopathy is caused by left ventricular hypertrophy (LVH).[3-5]

The National Kidney Foundation Task Force about CVD in CKD has emphasized the high risk of CVD in patients with CKD, and has identified LVH and coronary artery disease as the major targets for intervention.[6] Left ventricular hypertrophy is an independent predictor of mortality in dialysis patients.[4,6] Its prevalence is very high among patients with ES-CKD starting hemodialysis,[7] which suggests that it might be present in a large percentage of patients with CKD since early stages.

Despite the relevance of that topic, only a few studies have been carried out about the predialysis prevalence of LVH.[1,8] We found no report in the literature about that topic in the Brazilian population. Thus, this study aimed at assessing LVH in the CKD population under specialized treatment at five nephrological centers in Brazil.

Patients and Methods

This is a multicenter cross-sectional study assessing 309 patients with CKD, who had been under conservative treatment for at least three months. They were selected at five Brazilian centers specialized in CKD (Universidade Federal de São Paulo, Universidade de São Paulo, Universidade do Estado do Rio de Janeiro, Pontifícia

Universidade Católica do Paraná, and Universidade Federal de Juiz de Fora) over the year 2005. The study comprised clinically stable patients with estimated glomerular filtration rate (eGF) ranging from 15 to 60 mL/min, and aged from 18 to 80 years. The exclusion criteria were as follows: acute or chronic infection; autoimmune disease; active treatment with steroids or immunosuppressors; and malignancy. All participants provided written informed consent, which had been approved by the Committees on Ethics in Research of their respective institutions.

Data Collection

Demographical and clinical data were collected in the patients' medical records, and were as follows: age; sex; etiology of CKD. The eGF was calculate by use of the Cockroft and Gault formula.[9]

Blood samples were obtained during fasting for determining the following: creatinine; urea; lipids; hemoglobin; iron; ferritin; transferrin saturation; intact parathyroid hormone (reference value, 10–65 pg/mL); ultra-sensitive C reactive protein (US-CRP) (Beckman, Galway, Ireland); and soluble Fas (sFas) (detection limit, 8 pg/mL) (OptEIA, PharMingen, San Diego, CA, USA). The last two were measured at the same laboratory at Hospital do Rim of UNIFESP.

Echocardiography

Doppler echocardiography was performed in 309 patients, according to the recommendations of the American Society of Echocardiography. Left ventricular systolic function was analyzed through ejection fraction calculation with the Teichholz method and a lower limit defined as 55%. Left ventricular mass (LVM) was estimated with the expression: LVM (g) = 08 X {1.04 X [(LVID + IVST + PWT)3- (LVID)3]} x 0.6, where: LVM = left ventricular mass; LVID = left ventricular inner diameter; IVST = interventricular septum thickness; PWT = left ventricular posterior wall thickness. Left ventricular mass in relation to the patient's height is left ventricular mass index (LVMI) (g/m^2), which was considered normal when lower than 131 g/m^2 in men and lower than 100 g/m^2 in women.[12]

Statistical analysis

All variables were expressed as mean ± standard deviation, median (variation), and frequency. The patients were divided into two groups according to the presence of LVH. The groups were compared by using Mann-Whitney test or Student t test. The distribution of categorical variables between groups was analyzed by using the chi-square test or Fisher exact test, when appropriate. Multiple logistic regression was used to identify the factors associated with the presence of ventricular hypertrophy. All variables with a significance level of at least 0.10 in univariate analysis were included in multiple logistic regression analysis. The significance level adopted was $p < 0.05$. All statistical analyses were performed by using SPSS software for Windows (SPSS Inc., Chicago, IL, USA).

Results

The population studied was 54% male and 64% white. The prevalence of LVH was 53%, 22% of whom were women. Of those without LVH, 40% were women (Table 1). Diabetes mellitus was present in 35% of the patients in both groups. Of those with LVH, 60% were in stage-4 CKD. Ejection fraction was within the normal range for both groups as follows: 1) no LVH - women, 67%±10%, and men, 68%±12%; 2) with LVH - women, 66%±12%, and men, 67%±10%. Only 10% of the patients had systolic dysfunction.

The biochemical profile was as expected, in accordance with the recommendations of the Brazilian Society of Nephrology guidelines.[13] Serum calcium and phosphate were normal, and the intact parathyroid hormone (iPTH) in patients with LVH was higher than recommended. Hemoglobin was within the normal range. The lipid values were close to normal, although the LDL fraction was slightly increased in the group with LVH. Systolic blood pressure was elevated in patients with LVH (Table 2).

The mean values of inflammatory markers were elevated (Table 3), but the medians had a great variation. The CRP showed a tendency towards elevation in patients with LVH, unlike sFas, whose values were similar and showed a wide variation in both groups.

Multivariate logistic regression analysis adjusted to age indicated the following determinants for LVH: calcium; hemoglobin; and diastolic blood pressure (Table 4).

Discussion

Cardiovascular disease is the major cause of death in patients with CKD prior to dialysis.[14-16] Left ventricular hypertrophy is present in up to 75% of the patients starting renal replacement therapy.[17] This high LVH prevalence helps to keep mortality high and impairs the quality of life of that population.

Most of the patients assessed in this study were in stage 4 of CKD. Most patients with LVH were males; women did not show the same LVH prevalence,

especially in stage 3. Diabetes is considered an important mediator of CVD, but that did not apply to the patients of the present study, in which the prevalence was the same in both groups.

The parameters analyzed have shown that the patients were clinically stable. The treatment of dyslipidemia was based on diet and/or medications for reaching the target recommended by the guidelines of the Brazilian Society of Nephrology,[13] and the lipid profile was very satisfactory. Those data support the information that lipids do not play a central role in the development of CVD in that population. [4]

Inflammatory markers have been suggested to be good predictors of CV events in patients with ES-CKD. This is particularly true for serum CRP levels.[18-20] Fas is a membrane protein that belongs to the family of tumor necrosis factor receptors;[21] sFas accumulates in serum as renal disease progresses.[22] Recently, sFas has been reported to be an independent predictive factor of coronary disease in patients on chronic hemodialysis.[21] Although CRP tends to be higher in patients with LVH, the values have shown a wide variation, and the difference was not statistically significant. The sFas measurement showed no difference between the

Table 1 Characteristics of the patients with chronic kidney disease (CKD).

	Patients n (%)	Female n (%)	Male n (%)	CKD stage	DM
With LVH	164 (53%)	37 (22%)	127 (78%)	3 = 40% 4 = 60%	35%
No LVH	145(47%)	58 (40%)	87 (60%)	3 = 49% 4 = 51%	35%

DM = *diabetes mellitus*; LVH = left ventricular hypertrophy .

Table 2 Age and laboratory characteristics of the population studied (n = 309).

	No LVH n = 145	With LVH n = 164	p
Age (years)	a 55 ± 14	60 ± 13	< 0.01
eGF mL/min	32 ± 12	30 ± 11	0.19
Ca mg/dL	9.8 ± 0.9	9.3 ± 0.9	< 0.01
P mg/dL	3.8 ± 0.8	4 ± 0.9	0.04
iPTH pg/m	146 ± 111	198 ±164	< 0.01
Hb g/dL	12.8 ± 1.8	12.3 ± 1.8	0.04
Iron µg/dL	80 ± 25	77 ± 25	0.46
TSat %	29 ± 8	27 ± 7	0.21
Ferritin ng/mL	160 ± 181	127 ± 129	0.1
Cholesterol mg/dL	200 ± 48	203 ± 44	0.65
Trig mg/dL	173 ± 162	150 ± 64	0.12
SBP mmHg	133 ± 23	143 ± 27	< 0.01
DBP mmHg	78 ± 12	83 ± 16	< 0.01
Glucose mg/dL	125 ± 68	121± 64	0.68

a Mean ± SD; Ca = calcium; SBP = systolic blood pressure; eGF = estimated glomerular filtration rate; Hb = hemoglobin; iPTH = intact parathyroid hormone; LVH = left ventricular hypertrophy; P = phosphate; Trig = triglycerides; TSat = transferrin saturation; DBP = diastolic blood pressure

groups with and without LVH. All those data have suggested that, at least by using those markers, clinically stable patients before dialysis have not shown inflammation as a key mediator of LVH.

Strict control of blood pressure (BP) is known to be one of the best practices to prevent LVH.[23] Of all patients, 49% showed high systolic BP levels, and 34% showed high diastolic BP levels. Of those with LVH, 54% and 41% had increased systolic and diastolic BP levels, respectively. In addition, diastolic BP was an independent determinant of LVH. This is a worrying result, because BP control should no be a difficult target to be reached, at least for most patients, considering the existing therapeutic armamentarium. We insist in the importance of strict BP control as an efficient measure for preventing both LVH and CKD progression.[24]

Recent studies have shown that hemoglobin normalization does not benefit that population.[25,26] On the other hand, anemia is known to be an important promoting factor of LVH.[27] Our data have shown that hemoglobin values were within the normal range in the stage-4 population studied. However, hemoglobin was an independent determinant factor of LVH. Normal hemoglobin values (data not shown) were observed in 82% of the patients, in accordance with the recommendation of the guidelines.[28] On the other hand, 18% of the patients had hemoglobin levels below 11g/dL. Such results indicate the importance of an adequate evaluation and treatment of anemia in that population, since it is an important factor related to uremia that also contributes to LVH.[27,29]

Calcium and phosphate levels were within the normal range, but were different between the groups with and without LVH. Intact parathyroid hormone was also elevated in patients with LVH and was different from that in the group with no LVH. A correlation between mineral metabolism, hyperparathyroidism, and LVH has been suggested, although its mechanism has not yet been totally understood.[30] Hyperphosphatemia is recognized as a risk factor for CV mortality in the population with ES-CKD.[31] The mechanism linking hyperphosphatemia with CV mortality in patients on renal replacement therapy is not completely known; however, recent data have suggested that hyperphosphatemia could have a deleterious effect, causing LVH.[32,33] Gomes *et al*s. have reported that phosphate levels, even when within the normal range, have associated with a PTH elevation in patients with CKD prior to dialysis.[34] The present data have suggested that before dialysis those factors could be involved in determining LVH. Such data confirm the need for further studies on the correlation between changes in mineral metabolism and LVH since early CKD stages.

Table 3 Inflammatory markers

	No LVH	With LVH	p
CRP mg/L (n)	130	148	
Median (min-max)	0.32 (0.01-12.8)	0.46 (0.016- 6)	0.16
25-75 Percentile	0.13-0.68	0.19-1.09	
sFas pg/mL (n)	97	101	
Median (min-max)	2227 (124-2613)	1560 (108 - 3592)	0.85
25-75 Percentile	705-2193	547-2410	

CRP = C-reactive protein; LVH= left ventricular hypertrophy; sFas = soluble Fas.

Table 4 Multivariate logistic regression analysis

Variables	ß Coefficient	95% CI	p
Calcium (mg/dL)	0.54	0.39 – 0.76	< 0.01
Hb (g/dL)	0.84	0.71 – 0.99	0.04
DBP (mmHg)	1.05	1.02 – 1.07	< 0.001

DBP = diastolic blood pressure; Hb = hemoglobin; CI = confidence interval.

Coronary disease and LVH in patients with ES-CKD have been recognized as atypical presentations of heart disease.[23] The present study confirms that statement, adding that approximately 40% of the patients with LVH have stage-3 CKD, emphasizing the hypothesis that that alteration occurs early. It is worth noting that the literature on that topic focuses on patients with CVD and no renal disease, and guidelines about CVD in patients with CKD are based on opinions, not on evidence, showing the lack of information in that area.[23] The first step to reverse that is identifying and quantifying the magnitude of the problem. The challenge faced by physicians is to identify CKD and treat it aggressively.

In conclusion, in our study, the incidence of LVH was high even in a group of patients undergoing specialized treatment. The results have shown that some determinants are reversible factors. Thus, it is paramount that preventive measures for LVH are adopted and evaluated in regard to their efficacy in preventing LVH, to optimize the treatment of CKD as a whole.

References

1. Paoletti E, Bellino D, Cassottana P, Rolla D, Cannella G. A Left Ventricular Hypertrophy in Nondiabetic Predialysis CKD. Am J Kidney Dis. 2005; 46:320-327.
2. Sarnak MJ, Levey AS, Schoolwerth AC *et al.* Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003; 108:2154-69.
3. Silberberg JS, Barre PE, Prichard S, Sniderman AD. Impact of left ventricular hypertrophy on survival in end stage renal disease. Kidney Int.1989; 6:286-90.
4. Parfrey PS, Harnett JD, Griffiths SM *et al.* The clinical course of left ventricular hypertrophy in dialysis patients. Nephron. 1990; 55:114-20.
5. Levin A, Djurdjev O, Thompson C *et al.* Canadian Randomized Trial of Hemoglobin Maintenance to Prevent or Delay Left Ventricular Mass Growth in PatientsWith CKD. Am J Kidney Dis. 2005; 46:799-811.
6. Meyer KB, Levey AS. Controlling the epidemic of cardiovascular disease in chronic renal disease: Report from the National Kidney Foundation Task Force on Cardiovascular Disease. J Am Soc Nephrol. 1998; 9(Suppl12):S31-S42.
7. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995; 47:186-92.
8. McMahon LP, Roger SD, Levin A, Slimheart Investigators Group. Development, prevention, and potential reversal of left ventricular hypertrophy in chronic kidney disease. J Am Soc Nephrol. 2004; 15:1640-1647.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16:31-41.
10. Teichholz LE, Kreulen T, Herman M V, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol. 1976; 37:7-11.
11. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation. 1977; 55:613.
12. Savage DD, Garrison RY, Kannel WB *et al.* The spectrum of left ventricular hypertrophy in a general population sample: the Framingham study. Circulation. 1987; 75:26-33.
13. Diretrizes Brasileiras de Doença Renal Crônica: Prevenção da progressão da Doença Renal Crônica. J Bras Nefrol 2004; 26 Supl 1:1-14.
14. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998; 32(suppl 3):S112-9.
15. Weiner DE, Tighiouart H, Amin MG *et al.* Chronic kidney disease as a risk factor for cardiovascular disease and all cause mortality: A pooled analysis of community based studies. J Am Soc Nephrol. 2004; 15:1307-15.
16. Foley RN, Levin A. Cardiovascular Disease in Chronic Renal Insufficiency. Am J Kidney Dis. 2000; 36:24-30.
17. Dikow R, Adamczak M, Henriquez E, Ritz E. Strategies to decrease cardiovascular mortality in patients with end-stage renal disease. Kidney Int. 2002; 61 (Suppl 80):S5-S10.
18. Menon V, Wang X, Greene T *et al.* Relationship between C reactive protein, albumin, and cardiovascular disease in patients with chronic kidney disease. Am J Kidney Dis. 2003; 42:44-52.
19. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003; 107:363-9.
20. Iseki K, Tozawa M, Yoshi S, Fukiyama K. Serum C-reactive protein and risk of death in chronic dialysis patients. Nephrol Dial Transplant. 1999; 14:1956-60.
21. Herbert MJ, Masse M, Vigneault N *et al.* Soluble Fas is a marker of coronary artery disease in patients with end-stage renal disease. Am J Kidney Dis. 2001; 38:1271-6.
22. Perianayagam MC, Murray SL, Balakrishnan VS *et al.* Serum soluble Fas (CD95) and Fas ligand profiles in chronic kidney failure. J Lab Clin Med. 2000;136:320-7.
23. Berl T, Henrich W. Kidney-Heart Interactions: Epidemiology, Pathogenesis, and Treatment. Clin J Am Soc Nephrol. 2006;1:8-18.
24. Ruggenenti P, Perticucci E, Cravedi P *et al.* Role of remission clinics in the longitudinal treatment of CKD. J Am Soc Nephrol. 2008; 19:1213-24.
25. Drueke TB, Locatelli F, Clyne N *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006; 355:2071-84.

26. Singh AK, Szczech L, Tang KL *et al*. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355:2085-98.
27. Silverberg DS, Wexler D, Blum M *et al*. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000; 35:1737-44.
28. Bregman R, Pecoits Filho R. Faixa ideal da hemoglobina. J Bras Nefrologia 2007; 29(Supl4):17-8.
29. Zalunardo N, Levin A. Anemia and the heart in chronic kidney disease. Sem Nephrol. 2006; 26:290-5.
30. Walker MD, Silverberg SJ. Cardiovascular aspects of primary hyperparathyroidism. J Endocrinol Invest. 2008; 10:925-31.
31. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15:2208-18.
32. Achinger SG, Ayus JC. Left ventricular hypertrophy: is hyperphosphatemia among dialysis patients a risk factor? J Am Soc Nephrol. 2006; 12(Suppl3):S255-S261.
33. Galetta F, Cupisti A, Franzoni F *et al*. Left ventricular function and calcium phosphate plasma levels in uraemic patients. J Intern Med. 2005; 258:378-84.
34. Gomes CP, Silva MIB, Duarte MEL *et al*. Bone disease in patients with chronic kidney disease under conservative management. São Paulo Medical Journal 2005; 123:83-7.