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Inflammation and left ventricular hypertrophy in pre-dialysis chronic kidney disease patients

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ABSTRACT

Introduction: Patients with chronic kidney disease have greater mortality than the general population, mainly due to cardiovascular disease. Left ventricular hypertrophy, common in these patients, is also associated with increased mortality due to cardiovascular events.

The prevalence of left ventricular hypertrophy and cardiovascular disease is influenced by traditional and emerging risk factors, such as inflammation. The aim of our study was to investigate the relationship between left ventricular hypertrophy and inflammatory markers in pre-dialysis patients.

Subjects and Methods: This was a cross-sectional study into 69 pre-dialysis patients followed-up at our Low Clearance outpatient clinic. Several demographic, clinical, biochemical and inflammatory parameters were analysed. The prevalence of left ventricular hypertrophy was evaluated using the left ventricular mass index. The demographic, clinical, biochemical and inflammatory parameters analysed were compared in pre-dialysis patients with and without left ventricular hypertrophy. The relationship between inflammation and treatment with angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers and between inflammation and left ventricular mass index was also investigated.

Results: Patients with chronic kidney disease presented higher inflammatory parameters than controls: 0.82±1.04 *vs.* 0.4±0.25 mg/dl, p=0.03 for hs-CRP; 5.3±5.6 *vs.* 2.1±0.37 mg/dl, p=0.002 for IL-6; and 11.6±8.9 *vs.* 4.5±1.2 mg/dl, p=0.0001 for TNF-α. The prevalence of left ventricular hypertrophy in chronic kidney disease patients was 66.4%. Patients with left ventricular hypertrophy tended not to be treated with angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers (17/6 *vs.* 23/23; p=0.058) and presented higher levels of IL-6 (6.2 *vs.* 3.4 pg/ml; p=0.015). We found a statistically significant relationship between the left ventricular mass index and hs-CRP (r=0.244, p=0.043) and IL-6 (r=0.338, p=0.004) levels.

Conclusions: This study suggests that inflammation may contribute to the high prevalence of left ventricular hypertrophy in the pre-dialysis population.

Key-Words:
Chronic kidney disease; inflammation; left ventricular hypertrophy.

INTRODUCTION

Patients with chronic kidney disease (CKD) have an excess mortality, 10-30 times higher than the general population, mainly due to the higher prevalence of cardiovascular disease[1]. The increased risk begins during the earlier stages of CKD, before end-stage renal disease[2-4].

The Framingham study also showed that left ventricular hypertrophy (LVH) is associated with increased mortality due to cardiovascular events[5] and more recent research has also confirmed the prognostic value of LVH in CKD patients[6-8]. In these patients, the prevalence of cardiovascular disease and LVH are influenced by many traditional risk factors, such as age[9], level of renal function[8] and the presence of hypertension[9,10], diabetes[11] and anaemia[7,9]. Moreover, other emerging risk factors, such as inflammation and endothelial dysfunction, are associated with increased vascular disease[12]. Several recently published studies have demonstrated an association between inflammation and LVH[13-17]. Prevention and treatment strategies demand accurate knowledge and appropriate management of all risk factors.

The aim of our study was to investigate the relationship between LVH and inflammatory markers in a group of pre-dialysis CKD patients.

SUBJECTS AND METHODS

This was a cross-sectional study conducted at our hospital between August 2003 and December 2004.

We followed 69 patients (CKD stages 4 and 5)[18] from our Low Clearance outpatient clinic, who agreed to participate. The inclusion criteria were an estimated GFR (eGFR) lower than 30 ml/min/1.73m^2 body surface area [Modification of Diet in Renal Disease (MDRD) equation [19]]. Any clinical signs of infection, malignancy, chronic liver disease or psychiatric disease were exclusion criteria.

At baseline (first appointment to our clinic), a clinical history and a physical examination were performed and all medications registered. Several clinical, biochemical and inflammatory parameters were analysed: gender; age; weight; height; presence of diabetic nephropathy (DN); hypertension; coronary artery disease (CAD); eGFR; haemoglobin (Hb); iron; ferritin; creatinine; blood urea nitrogen (BUN); uric acid; albumin; pre-albumin; cholesterol (total and HDL); triglycerides; uric acid; calcium (Ca); phosphate (Pi); calcium phosphate product (Ca x Pi); intact parathormone (iPTH); IL-6; hs-CRP and TNF-α. The GFR was calculated using the MDRD formula[19].

Blood pressure was measured following Perloff's recommendations[20]. Hypertension was considered present when the resting blood pressure (BP) was higher than 140/90 mmHg or when, regardless of BP values, the patient was under antihypertensive therapy. CAD was defined by a history of classical exertional angina, myocardial infarction, coronary percutaneous angioplasty or by-pass grafting[21]. Asymptomatic CAD was also considered whenever there was a positive result on a treadmill stress test, with echocardiography, myocardial scintigraphy or coronariography[21].

Baseline two-dimensional and M-mode echocardiography were performed with a 3-Mhz transducer by an independent observer. All patients were observed in a left lateral decubitus position. Parameters such as left ventricular end-diastolic diameter, posterior left ventricular wall thickness and the interventricular septum thickness in diastole were recorded. The left ventricular mass (LVM) was calculated using the Penn convention criteria[22] and was divided by the body surface area (Gehan and George equation)[23], to compute the left ventricular mass index (LVMI) in g/m^2. LVH was considered present when the LVMI was greater than 110 g/m^2 in women and greater than 130 g/m^2 in men.

Plasma, collected using heparin as anticoagulant, was separated (within 30 minutes of drawing) and stored at -80º C until analysis for the measurements of chemiluminescent immunometric assay (Immulite® 2000 High Sensitivity CRP) and IL-6 and TNF-α (solid–phase, enzyme labelled, chemiluminescent sequential immunometric assay, Immulite®).

Darbepoetin alfa was given subcutaneously in all patients. All patients receiving darbepoetin alfa were under iron therapy.

Our control group consisted of a population of blood donors. Written and informed consent was obtained from all patients and the study was approved by the local ethics committee.

Study design and statistical analysis

The inflammatory parameters of CKD patients were compared with those of the control group. Our

population of CKD patients was then divided into 2 groups, G I, patients without LVH and G II, patients with LVH, which were then compared as to the several parameters described above. The relationship between inflammation and medication with ACEIs and or ARBs and between inflammation and LVMI was also investigated.

Student's *t*-test, Mann-Witney and Chi-square test were used for comparisons between groups. A linear regression model was used to evaluate the relationship between the LVMI (dependent variable) and the inflammatory parameters (independent variables). The statistical analysis was performed with SPSS 11.0 for Windows (SPSS, Inc. Chicago, IL). Data are expressed as mean±SD or median and range for variables not normally distributed. The null hypothesis was rejected below the 5% level.

RESULTS

We studied 69 patients (31 female and 38 male) followed-up at our Low Clearance outpatient clinic, mean age 68.4±15.5 years, eGFR 15.8±6.9 ml/min (Table I). The main causes of CKD (56%) were diabetic nephropathy (n=25) and hypertensive renal disease (n=14) (Table I). The majority of our patients were hypertensive (80%) with ACEIs and/or ARBs used as part of the therapeutic strategy in 58% (Table I). The mean LVMI was 153.7±49.3g/m^2 with 66.4% of patients presenting LVH (Table I). The mean Hb level was 11.3±1.6 g/dl with almost all patients (88.4%) treated with darbepoetin alfa (0.544±0.51μg/kg/w) (Tables I and II).

The levels of all inflammatory parameters were significantly higher in CKD patients than in the control group: 0.82±1.04 *vs.* 0.4±0.25 mg/dl, p=0.03 for hs-CRP; 5.3±5.6 *vs.* 2.1±0.37 mg/dl, p=0.002 for IL-6; and 11.6±8.9 *vs.* 4.5±1.2 mg/dl, p=0.0001 for TNF-α (Table III).

Patients with LVH (G II) showed a trend to be older (70.3±15.0 *vs.* 64.8±16.2 years; p=ns) and towards treatment with a higher darbepoetin alfa dose (0.597±0.54 *vs.* 0.439±0.84 μg/kg/w; p=ns), despite similar haemoglobin levels (11.2±1.7 *vs.* 11.4±1.6 g/dl; p=ns) (Table IV). There were a higher

Table I

Demographic, clinical and cardiovascular data of the CKD patients

Gender (m/f)	38/31
Age (years)	68.4±15.5
Causes of CKD:	
• Diabetic nephropathy	25
• Hypertensive renal disease	14
• Chronic interstitial nephritis	8
• Chronic glomerulonephritis	4
• Polycystic kidney disease	2
• Unknown	16
Darbepoetin α (μg/kg/w)	0.544±0.51
Hypertension (y/n)	56/13
Medication ACEIs and/or ARBs (y/n)	40/29
CAD (y/n)	16/53
LVMI (g/m^2)	153.7±49.3
LVH (y/n)	46/23

Table II

Biochemical and inflammatory parameters of the CKD patients

BUN (mg/dl)	73.0±27.0
Creatinine (mg/dl)	5.4±3.8
eGFR (ml/min)	15.8±6.9
Haemoglobin (g/dl)	11.3±1.6
Iron (μg/dl)	64.0±36.0
Ferritin (ng/ml)	152.0±187.0
Ca (mg/dl)	9.7±1.1
Pi (mg/dl)	4.9±1.6
Ca x Pi (mg^2 /dl^2)	48.0±16.0
iPTH (pg/ml)	339.0±265.0
Uric Acid (mg/dl)	8.4±2.5
Total Cholesterol (mg/dl)	207.0 ±56.0
HDL Cholesterol (mg/dl)	50.0±21.0
Triglycerides (mg/dl)	146.0±74.0
Albumin (g/dl)	4.2±0.5
Pre-Albumin (mg/dl)	31.5 ± 8.6
TNF-α (pg/ml)	11.6 (1.3 - 65.9)*
IL-6 (pg/ml)	3.7 (2 - 42.6)*
hs-CRP (mg/dl)	0.4 (0.02 - 5.6)*

*data presented as median and range

Table III

Inflammatory parameters of CKD patients *vs.* control group

	CKD Patients (n=69)	Control Group (n=30)	p
hs-PCR (mg/dl)	0.82±1.04	0.4±0.25	0.03
IL-6 (pg/ml)	5.3±5.6	2.1±0.37	0.002
TNF-α (pg/ml)	11.6±8.9	4.5±1.2	0.0001

proportion of female patients (21/25 *vs.* 6/17; p=0.039) in G II. A similar number of hypertensive patients were observed in both groups but in G II there was a strong trend towards a lower proportion of patients being treated with ACEIs and/or ARBs (17/6 *vs.* 23/23; p=0.058) (Table IV). Finally, patients in G II presented higher levels of IL-6 (6.2 *vs.* 3.4 pg/ml; p=0.05) but only a trend to have higher levels of hs-CRP (0.44 *vs.* 0.31 mg/dl; p=0.039) (Table IV).

Table IV

Comparison of non-LVH (G I) and LVH patients (G II)

	G I (n=23)	G II (n=46)	p
Age (years)	64.8±16.2	70.3±15.0	ns
Gender (f/m)	6 / 17	21 / 25	0.039
Hypertension (y/n)	21 / 2	35 / 11	ns
ACEIs and/or ARBs (y/n)	17/6	23/23	0.058
Diabetic nephropathy (y/n)	8 / 15	17 / 29	ns
Haemoglobin (g/dl)	11.2±1.7	11.4±1.6	ns
Darbepoetin α (µg/kg/w)	0.439±0.84	0.597±0.54	ns
eGFR (ml/min)	15.4±6.8	16.0±7.8	ns
BUN (mg/dl)	76.0±21	71.0±29.0	ns
Ca (mg/dl)	9.8±0.9	9.7±1.1	ns
Pi (mg/dl)	5.1±1.7	4.7±1.5	ns
Ca x Pi (mg^2 /dl^2)	51.0±18	47.0±15.0	ns
PTH (pg/ml)	332.0±204.0	342.0±293.0	ns
Albumin (g/dl)	4.2±0.6	4.2±0.5	ns
Pre-albumin (mg/dl)	32.0±7.0	31.0±9.3	ns
LVMI (g/m^2)	108.0±15.0	177.0±44.0	0.001
IL-6 (pg/ml)	3.4 (2 - 8)*	6.2 (2- 42.6)*	0.015**1
hs-CRP (mg/dl)	0.315 (0.05-2.05)*	0.44 (0.02-5.6)*	0.175**2
TNF-α (pg/ml)	8.6 (2.4-65.9)	11.25 (1.3-35.2)*	0.196**3

*data presented as median and range

**1 – Z = - 2.442; **2 – Z = - 1.356; **3 – Z =- 1.292 (Mann-Witney test)

We also found a significant relationship between the LVMI and hs-CRP (r=0.244, p=0.043) and IL-6 (r=0.338, p=0.004) levels (Figures 1 and 2). No differences were found in the levels of inflammatory parameters between patients treated and non-treated with ACEIs and/or ARBs (Table V).

Table V

Inflammatory parameters of CKD patients treated and non-treated with ACEIs and/or ARBs

	Treated (n=40)	Non-treated (n=29)	p
hs-PCR (mg/dl)	0.88±0.9	0.75±1.2	ns
IL-6 (pg/ml)	5.1±3.9	5.6±7.4	ns
TNF-α (pg/ml)	11.9±10.9	11.2±5.1	ns

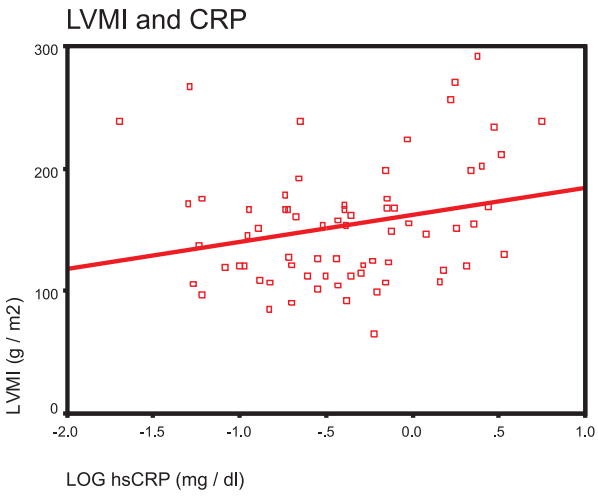

Figure 1

Positive correlation between Log hs-CRP and LVMI (r=0.244; p=0.043)

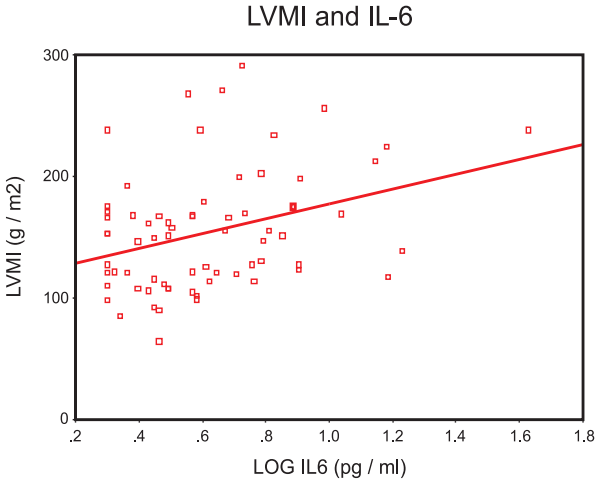

Figure 2

Positive correlation between Log IL-6 and LVMI (r=0.338; p=0.004)

DISCUSSION

Cardiovascular disease is the leading cause of morbidity and death in CKD patients[1]. LVH is an important risk factor of morbidity and mortality in the general[5] as well as the CKD population[6-8].

The high prevalence of LVH observed in our patients can be explained by advanced age and the

severity of renal impairment. This prevalence is similar to that reported by Parfrey *et al.*[24] (68%) and greater than that reported by Greaves *et al.*[25] (39%), but the mean age of our population (68.4 *vs.* 46 and 50 years, respectively) is quite higher. Nevertheless, it is important to remember that those studies only included patients on chronic dialysis[24-25]. Conversely, and as expected, the prevalence of LVH in the present study is lower than that we previously reported involving an elderly haemodialysis population (73%)[9].

Hypertension[9,10] and diabetes[11], well-known risk factors of LVH, were not associated with the presence of LVH in our population. In CKD patients, it is already well established that blood pressure values are inversely correlated with morbidity and mortality[26-27], *the reverse epidemiology phenomenon*[28]. To calculate the LVMI we used the left ventricular end-diastolic diameter (LVEDD), liable to be increased in patients with dilated cardiomyopathy, which in turn is associated with low blood pressure values. This fact could, at least partially, explain the lack of association between hypertension and LVH. The explanation for diabetes seems to reside in the fact that our diabetic patients showed higher GFRs than those without diabetes (17.4 *vs.* 14.9 ml / min), with renal function being a predictor of LVMI and LVH[8].

Despite no differences in the mean LVMI between genders (157.9 *vs.* 150.2 g/m^2 ; p=ns, for female and male patients), we found a higher proportion of females in G II. We think that the definition of LVH *per se* can account for this fact: an LVMI of 110 g/m^2 in women and 130 g/m^2 in men.

Over the last few years inflammation has also emerged as a risk factor of morbidity and mortality in the general[29-31] and CKD population[32-35]. The prevalence of inflammation is high in CKD patients, as mirrored by the elevated levels of CRP and pro-inflammatory cytokines[35]. This uraemic inflammatory status[34-37] can be explained by the reduced renal clearance of the inflammatory markers, the accumulation of AGEs, the presence of atherosclerosis and heart failure, and the higher prevalence of bacterial or viral infections[38,39] observed in this population. Consequently, as expected, our CKD patients presented higher levels of the inflammatory parameters than the control group. Similarly to other researchers, we were able to demonstrate a relationship between inflammation and LVH. Erten *et al.*[13] observed in a group of haemodialysis patients that the LVMI was correlated with TNF-α levels and Wang *et al.*[40] found, also in a haemodialysis population, that CRP was a risk factor of LVH. In CKD pre-dialysis populations, Ates *et al.*[41], Matteuci *et al.*[15], and Cottone *et al.*[17] also described the association between CRP and LVMI. Even in the setting of kidney transplantation such an association was observed by Franek *et al.*[14]. Like us, several authors have reported IL-6 as the link between inflammation and cardiovascular disease. In fact, an association of IL-6 gene polymorphisms with cardiovascular disease in the general population[42] and more recently an association between the IL-6 promoter polymorphism, 174G/C and LVH in haemodialysis patients[43] has been demonstrated. Pecoits-Filho *et al.*[44] also reported an association between LVM and IL-6 levels in a population of CKD patients close to the start of dialysis. Fredj *et al.*[45] recently showed that IL-6 can induce myocyte hypertrophy by an autocrine pathway and fibroblast proliferation by a paracrine pathway, and these effects could be mediated by angiotensin II.

Therapeutic strategies targeting inflammation, such as ACEIs and/or ARBs, statins, anti-oxidant agents, and more recently vitamin D, have also proven to reduce left ventricular hypertrophy[46,47].

In conclusion, we found a high prevalence of LVH in our CKD patients, which was associated with inflammation. Since both contribute to the high morbidity and mortality in the CKD population, every attempt must be made to correct them.

Conflict of interest statement. None declared.

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