ORIGINAL ARTICLE

Association of glomerular filtration rate and inflammation with left ventricular hypertrophy in chronic kidney disease patients

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Abstract

Background: Although left ventricular hypertrophy (LVH) is an independent predictor of mortality in patients with end stage renal disease, few have examined its prevalence before the initiation of dialysis. The aim of this study was to investigate the relationship between LVH, estimated glomerular filtration rate (GFR), and inflammatory markers in patients with chronic kidney disease (CKD).

Methods: Forty-one CKD patients (18 women, 23 men, mean age 53±17 years) with an estimated GFR between 15 and 59 mL/min (mean 34.2 mL/min) were enrolled and the following tests performed: routine serum biochemical analyses, high sensitivity C-reactive protein (hs-CRP), fibrinogen, ferritin, and homocysteine, and left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF), and left ventricular fractional shortening (LVFS).

Results: LVH was diagnosed in 32/41 patients (78%). CKD patients with LVH (n=32) had significantly higher hs-CRP (p=0.012), fibrinogen (p=0.031), and lower serum albumin (p=0.028) levels than those without LVH (n=9). In all patients, LVMI correlated positively with hs-CRP (r=0.483, p=0.002) and serum fibrinogen (r=0.426, p=0.015). Estimated GFR correlated positively with LVEF (r=0.414, p=0.007) and LVFS (r=0.376, p=0.018).

Conclusions: Important positive associations exist between markers of inflammation and LVMI in patients with CKD. In addition to hs-CRP, elevated fibrinogen may portend the development of LVH in patients with CKD who are not yet on dialysis. Hippokratia 2012; 16 (2): 137-142

Key words: chronic kidney disease, echocardiography, fibrinogen, hs-CRP, left ventricular hypertrophy

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Patients with end stage renal disease (ESRD) are at high risk for vascular atherosclerosis and left ventricular hypertrophy (LVH)[1,2]. LVH is an independent predictor of cardiovascular mortality in patients with ESRD and appears to progress during dialysis therapy[3-5]. The high prevalence of LVH among ESRD patients at the start of dialysis therapy[6] suggests that it might already be present in a significant proportion of chronic kidney disease (CKD) patients who are not yet on dialysis[7].

Hypertension, hypervolemia, and anemia have been identified as major determinants of LVH in ESRD patients[4,6]. Other factors such as inappropriate activation of the renin-angiotensin-aldosterone system, oxidative stress, and inflammation may also play a role in left ventricular growth in ESRD[8]. Persistent activation of the inflammatory response has been recognized as an important independent risk factor for the development of cardiovascular complications in hemodialysis patients[9]. Levels of C-reactive protein (CRP), a marker of the reactant plasma protein component, correlate positively with LVH in patients receiving hemodialysis[10,11]. However, the number of studies examining the association between inflammatory markers and LVH in patients with CKD is limited.

In patients with CKD not yet on dialysis, the decline in creatinine clearance was associated with an increase in the left ventricular mass index[12]. Studies of LVH in CKD patients found that its prevalence increases with declining renal function[7,12,13]. Regression of LVH was noted in dialysis patients after successful kidney transplantion[14]. Both of these observations suggest that renal dysfunction is an important factor in the development of LVH.

The aim of this study was to investigate the relationship between estimated glomerular filtration rate (GFR), inflammatory markers, and left ventricular hypertrophy (LVH) in patients with CKD.

Subjects and methods

Patients

The study protocol was approved by our Faculty of Medicine Ethics Committee. Between June 2008 and December 2009, patients over 18 years old with CKD managed without dialysis presenting to our university hospital outpatient nephrology clinic were approached for participation in the study. Participation was allowed if creatinine clearance was between 15 and 59 mL/min and if they had carried a diagnosis of CKD for at least 3

Table 1: Demographic, clinical and laboratory characteristics of 41 patients with chronic kidney disease. Values are expressed as mean±SD unless otherwise noted.

	n=41
Age, *years*	53±17
Percent female	44
Smoking status (yes/no) (%)	42/58
Cause of CKD, n (%)	
Diabetic nephropathy	8 (20)
Hypertensive nephrosclerosis	7 (17)
Reflux nephropathy	5 (12)
Chronic glomerulonephritis	4 (10)
Polycystic kidney disease	1 (2)
Chronic tubulointerstitial nephritis	1 (2)
Unknown	15 (37)
Duration of disease, *months*	25±37
Systolic blood pressure, *mmHg*	130±17
Diastolic blood pressure, *mmHg*	81±10
Mean arterial blood pressure, *mmHg*	97±12
Hemoglobin, *g/dL*	12.2±1.5
Blood urea nitrogen, *mg/dL*	42±18
Serum creatinine, *mg/dL*	2.5±0.9
Estimated GFR, *mL/min*	34.2±9.8

months. Exclusion criteria included cancer, autoimmune disease, or any other known condition that would alter inflammatory status or use of medications such as cimetidine, trimethoprim or amiloride, which can affect estimated GFR by altering plasma creatinine concentration[15]. Patients who had atrial fibrillation or severe ischemic heart disease with abnormal left ventricular wall motion or severe valvular heart disease by echocardiography were also excluded. All patients gave written informed consent before entering the study.

Demographic data were obtained, including age, gender, and tobacco usage. Antihypertensive medications prescribed previously were recorded; multiple agents of a single class (eg. angiotensin-converting enzyme inhibitors, beta-adrenergic antagonists) were coded as one agent unless they have recognized clinical utility in combination (eg. calcium channel antagonists).

Laboratory parameters

After fasting overnight, between 08.00 and 10.00 in the morning, venous blood samples were drawn from the antecubital vein of all patients before echocardiography was performed. For fibrinogen measurement, a sample was separately taken into an EDTA tube. Blood urea nitrogen (BUN), creatinine, hemoglobin concentration, serum albumin, cholesterol, triglycerides, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol levels were analyzed using standard laboratory methods. High sensitivity C-reactive protein (hs-CRP), fibrinogen, ferritin, and homocysteine levels were also measured. Hs-CRP was measured by immunonephelometry on an Image 800 Immunochemistry System (Beckman Coulter Inc, Fullerton, USA). Plasma fibrinogen was measured by clotting with a commercially available kit (Albio, Diagnostica Stago, Seine, France). Serum ferritin was measured by electrochemilluminescence immunoassay with a Roche E-170® automatic analyzer (Hitachi Corporation, Osaka, Japan). Homocysteine levels were measured by a high-pressure liquid chromatography (HPLC) using a commercial kit (Recipe, Chemicals & Instruments, GmbH, Munich, Germany). Intact parathyroid hormone levels and quantitative total protein measurements in 24-h urine samples were obtained from patient files.

Renal function was determined by estimating GFR with the Cockroft and Gault formula[16] using the serum creatinine concentration (Cr_s, mg/dL) as follows:

GFR in males (mL/min) = [(140 – age) x body weight] / (Cr_s x 72)

GFR in females (mL/min) = value for males x 0.85.

Echocardiography

Transthoracic echocardiography was performed on patients in the left decubitus position with a Vivid 7 Dimension ultrasound machine with a 3.5 MHz probe (GE Healthcare, Milwaukee, USA). A single experienced cardiologist (G.K.), blinded to the clinical details of the patients, made the M-mode echocardiographic measurements. Left ventricular mass (LVM, calculated by the Devereux formula[17]) was corrected by body surface area and expressed as LVM index (LVMI). Left ventricular hypertrophy was defined as LVMI >131 g/m^2 for men and >100 g/m^2 for women[18]. Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) were calculated by using the Teichholz method. Blood pressures of the patients were measured from the right arm by a manual sphygmomanometer at the time of echocardiography, after 10 minutes of rest.

Statistical analysis

Data were evaluated using SPSS version 13.0 for Windows® (SPSS Inc., Chicago, USA). Comparisons between groups were performed using Student-*t* test for normally distributed variables, whereas the Mann-Whitney U test was used for parametric variables with non-normal distributions. Chi-square testing was used to analyze categorical data. Correlations between estimated GFR and clinical, biochemical and echocardiographic parameters were investigated by Spearman's correlation test. A p value of <0.05 was considered statistically significant.

Results

Forty-one patients (18 women, 23 men, mean age 53±17 years) participated in the study. Demographic and clinical characteristics of the patients are given in Table

Table 2: Characteristics and echocardiographic measurements of the 41 study subjects, stratified according to level of kidney function: stage 3 if the estimated GFR was 30-59 mL/min, and stage 4 if the estimated GFR was 15-29 mL/min. Values are expressed as mean±SD unless otherwise noted. Statistically significant values are italicized.

	Stage 3 (*n*=26)	**Stage 4 (*n*=15)**	***P***
Age, *years*	54±17	51±16	0.659
Percent female, *n* (%)	12 (46)	6 (40)	0.702
Duration of disease, *months*	33±44	12±10	0.314
Systolic blood pressure, *mmHg*	128±17	134±18	0.341
Diastolic blood pressure, *mmHg*	80±10	83±10	0.369
Mean arterial blood pressure, *mm Hg*	97±12	100±12	0.149
Number of anti-hypertensive medications	1.6±0.8	1.7±1.0	0.952
Hemoglobin, *g/dL*	12.7±1.3	11.4±1.5	*0.008*
Serum albumin, *g/dL*	4.4±0.4	4.1±0.5	*0.034*
Intact parathormone, *pmol/L*	113±59	241±400	0.383
Blood urea nitrogen, *mg/dL*	34±12	56±18	*<0.001*
Serum creatinine *mg/dL*	2.0±0.5	3.2±0.8	*<0.001*
Hs-CRP, *mg/dL*	0.5±0.6	1.8±3.0	0.317
Fibrinogen, *g/L*	4.7±1.0	5.0±1.2	0.478
Ferritin, *ng/mL*	88±72	204±260	*0.041*
Homocysteine, *mg/dL*	25±12	21±9	0.389
Estimated GFR *mL/min*	40.8±8.1	23±3.3	*<0.001*
LVMI, g/m^2	158±58	149±41	0.904
LVEF	71±12	66±7	*0.013*
LVFS	42±9	38±5	0.160

GFR, glomerular filtration rate; Hs-CRP, high sensitivity C reactive protein; LVMI, Left ventricular mass index; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening

I. The mean estimated GFR of the study cohort was 34.2 mL/min. Table II shows the clinical characteristics of patients stratified according to the level of renal function. By kidney disease outcome quality initiative (K/DOQI) guidelines, 63% (26 patients) had stage 3 and 37% (15 patients) had stage 4 CKD[19]. Patients with stage 4 CKD had a lower LVEF (66±7%) than patients with less severe CKD (71±12%, p=0.013). Stage 3 and stage 4 CKD patients did not differ significantly with regard to LVMI (p=0.904) and LVFS (*P*=0.160).

In patients with CKD, the mean LVMI was 154±52 g/m^2 (range 60–307 g/m^2) and LVH was diagnosed in 32 patients (78%). These patients with LVH had significantly higher hs-CRP (*P*=0.012), fibrinogen (p=0.031) and lower albumin (p=0.028) levels than those without LVH (n=9). However, estimated GFR (p=0.865), and daily protein excretion (p=0.106) were not significantly different between the two groups, as shown in Table III. Patients with and without LVH were not significantly different with respect to serum ferritin (p=0.772) and homocysteine levels (p=0.134). In the entire cohort, LVMI correlated positively with hs-CRP (r=0.483, p=0.002) and serum fibrinogen (r=0.426, p=0.015).

In CKD patients, estimated GFR correlated positively with hemoglobin (*r*=0.444, p=0.004), and serum albumin (r=0.441, p=0.004), as shown in Table IV. Estimated GFR was significantly and inversely related to mean arterial blood pressure (r=-0.384, p=0.013), serum ferritin (r =-0.334, p=0.038) and serum parathyroid hormone levels (r=-0.343, p=0.032). Importantly, estimated GFR correlated positively with LVEF (r=0.414, p=0.007) and LVFS (r=0.376, p=0.018) but not to LVMI (r=0.083, p=0.607). Among patients with LVH (n=32), estimated GFR also correlated with LVEF (r=0.388, p=0.028) and LVFS (r=0.383, p=0.033), but not to LVMI (r=0.157, p=0.392).

Discussion

In this cross-sectional study, patients with CKD who had more kidney dysfunction had a lower mean LVEF. In the entire cohort, estimated GFR was positively correlated with LVEF and LVFS. CKD patients with LVH had sig-

Table 3: Characteristics and echocardiographic measurements of the 41 CKD patients, stratified according to the presence of left ventricular hypertrophy (defined as left ventricular mass index of >131 g/m^2 for men and >100 g/m^2 for women). Values are expressed as mean±SD unless otherwise noted. Statistically significant values are italicized.

	with LVH (*n*=32)	without LVH (*n*=9)	*P*
Age, *years*	55±16	45±15	0.470
Percent female, *n*(%)	15 (47)	3 (33)	0.470
Systolic blood pressure, *mmHg*	131±19	129±12	0.769
Diastolic blood pressure, *mmHg*	83±10	76±7	0.075
Mean arterial blood pressure, *mm Hg*	98±13	93±8	0.841
Number of anti-hypertensive medications	1.7±0.9	1.6±0.5	0.929
Hemoglobin, *g/dL*	12.1±1.6	12.6±0.9	0.410
Serum albumin, *g/dL*	4.2±0.4	4.5±0.4	*0.028*
Hs-CRP, *mg/dL*	1.2±2.1	0.2±0.2	*0.012*
Fibrinogen, *g/L*	5.0±1.0	4.0±0.2	*0.031*
Ferritin, *ng/mL*	144±196	89±56	0.772
Homocysteine, *mg/dL*	24±10	19±12	0.134
Estimated GFR, *ml/min*	34±10	36±15	0.865
24-hour urine protein, *mg/24 hr*	1300±1421	657±1100	0.106
LVMI, *g/m^2*	170±48	100±21	*<0.001*
LVEF	69±12	69±9	0.841
LVFS	40±9	41±3	0.810

GFR, glomerular filtration rate; Hs-CRP, high sensitivity C reactive protein; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening

nificantly lower levels of serum albumin and higher levels of hs-CRP and fibrinogen compared to their non-LVH counterparts. LVMI correlated positively with hs-CRP and serum fibrinogen. Since serum albumin is a negative acute-phase reactant, and hs-CRP and fibrinogen are biomarkers of inflammation, our results demonstrate that mean left ventricular mass in CKD patients increases in parallel with the degree of inflammation.

In this study, LVH was present in 78% of CKD patients, a higher proportion than is usually reported in renal patients[12,20,21]. The high prevalence of LVH in our study cohort may be due to our inclusion of diabetic patients, who are known to have a higher prevalence of vascular disease and cardiac hypertrophy than the normal population[22]. However, similar to our findings, the recent study by Paoletti et al. also reported a high prevalence (78%) of LVH in their population of stage 3, 4, and 5 CKD patients[7].

Inflammation, as demonstrated by low serum albumin and high hs-CRP and fibrinogen levels, appears to play an important role in the development of LVH in CKD patients. Elevated CRP levels and hypoalbuminemia is associated with progressive LVH in dialysis patients[10,11,23,24]. In 2007, Cottone et al. was the first to report the positive correlation (r=0.58, P<0.0001) between left ventricular mass index and hs-CRP in patients with moderate CKD[25]. They also showed that levels of fetuin-A, which is a negative acute phase reactant like albumin[26], were inversely correlated with LVMI (r=-0.41, p=0.001). We did not measure fetuin-A levels, but measured other markers of cardiovascular risk such as fibrinogen and homocysteine.[27] To date, only one study of dialysis patients has been published which reported the association between serum fibrinogen and LVH[28]. The current study is the first to describe the relationship between left ventricular mass index and serum fibrinogen in patients with CKD who are not yet on dialysis. Thus, we feel that malnutrition and inflammation should be added to the list of well-known risk factors (hypertension, extra-cellular fluid volume expansion and anemia) for the development of LVH in patients with CKD, as is the case of patients on dialysis[25,29,30].

Chronic kidney disease patients with malnutrition are known to exhibit elevated plasma inflammatory cytokine levels, which may in turn cause poor nutritional status and trigger cardiovascular co-morbidities[26,29]. These patients should be followed with the counseling of a dietitian from the early stage of renal disease to prevent malnutrition. Several pathophysiological mechanisms by which inflammation might contribute to development of ventricular hypertrophy have been proposed[31]. Inflamma-

Table 4: Correlation between estimated glomerular filtration rate (GFR, mL/min) and clinical, laboratory, and echocardiographic parameters in 41 CKD patients. Statistically significant values are italicized.

	r	*P*
Age	0.007	0.964
Duration of disease, months	0.100	0.535
Systolic blood pressure, *mmHg*	-0.297	0.059
Diastolic blood pressure, *mmHg*	-0.266	0.093
Mean arterial blood pressure, *mm Hg*	-0.384	*0.013*
Hemoglobin, *g/dL*	0.444	*0.004*
Blood urea nitrogen, *mg/dL*	-0.741	*<0.001*
Creatinine, *mg/dL*	-0.774	*<0.001*
Serum albumin, *g/dL*	0.441	*0.004*
Serum hs-CRP, *mg/dL*	0.028	0.867
Fibrinogen, *g/L*	-0.066	0.719
Ferritin, *ng/mL*	-0.334	*0.038*
Intact parathormone, *pmol/L*	-0.343	*0.032*
Homocysteine, *mg/dL*	0.122	0.486
LVMI, g/m^2	0.083	0.607
LVEF	0.414	*0.007*
LVFS	0.376	*0.018*

Hs-CRP, high sensitivity C reactive protein; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening

tion may promote the development of LVH via changes in morphology and function of vascular smooth muscle cells which increase arterial stiffness[31,32]. In addition, subclinical inflammation can lead to adverse left ventricular geometry by altering the equilibrium that regulates cell growth, apoptosis, phenotype, and matrix turnover of cardiac tissue[31].

In this study, estimated GFR was positively correlated with LVEF and LVFS, suggesting a close relationship between the degree of renal function and left ventricular systolic function. However, we could not demonstrate a correlation between estimated GFR and LVMI either in the entire cohort or in the subgroup of patients with LVH. Conversely, two consecutive studies by Levin et al., with larger numbers of patients, clearly demonstrated an increase in the prevalence of LVH as renal function (defined by low creatinine clearance) decreased[12,20]. In our study, a larger patient population may have resulted in the detection of a clear relationship between low estimated GFR and high LVMI.

Timed (24-hour) urine collections have long been used clinically to measure creatinine clearance, and, hence GFR[33]. Difficulties in obtaining reliable 24-hour urine specimens account for the imprecision of this test. Errors resulting from under-collection or over-collection of urine introduce significant mistakes in calculated creatinine clearance.[33] For these reasons, we used the Cockroft-Gault equation to estimate GFR, which is a more sensitive marker and accurate measure of renal function[34].

Limitations of this study include its relatively small sample size (n=41) and its cross-sectional design. While causality cannot be proven in cross-sectional studies, associations can be demonstrated. Another limitation of this study is our inclusion of patients with CKD secondary to systemic hypertension, which itself is a well-known predisposing factor for LVH. We also failed to test for the presence of other pathology associated with LVH, such as myocardial ischemia.

In summary, we found important positive associations between LVMI and markers of inflammation such as hs-CRP and fibrinogen in patients with CKD. In addition to hs-CRP, elevated fibrinogen was associated with cardiac hypertrophy and dysfunction in patients with CKD not yet on dialysis. Clinical studies should be performed in CKD patients to evaluate the effects of anti-inflammatory treatments on the development of cardiac hypertrophy and dysfunction.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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