Associations Between Albuminuria, Estimated GFR and Cardiac Phenotype in a Cohort with Chronic Kidney Disease: The CPH-CKD ECHO Study

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ABSTRACT

Objective: Echocardiographic findings in chronic kidney disease (CKD) vary. We sought to estimate the prevalence of abnormal cardiac structure and function in patients with CKD and their association to estimated glomerular filtration rate (eGFR) and urine albumin/creatinine ratio (UACR).

Methods: We prospectively enrolled 825 outpatients with non-dialysis-dependent CKD, mean age 58±13 yrs, and 175 matched healthy controls, mean age 60±12 yrs. Echocardiography included assessment of left ventricular (LV) hypertrophy, LV ejection fraction (LVEF), global longitudinal strain (GLS) and diastolic dysfunction according to ASE/EACVI guidelines.

Results: LV hypertrophy was found in 9% of patients vs. 1.7% of controls (p=0.005) was independently associated with UACR (p=0.002). Median LVEF was 59.4% (IQR 55.2, 62.8) in patients vs. 60.8% (57.7, 64.1) in controls (p=0.002). GLS was decreased in patients with eGFR <60ml/min/1.73m² (-17.6%±3.1%) vs. patients with higher eGFR (19.0%±2.2%, p<0.001), who were similar to controls. Diastolic dysfunction was detected in 55% of patients and in 34% of controls.

Limitations: Non-random sampling, cross-sectional analysis.

Conclusions: We report lower prevalence of hypertrophy than previous studies, but similar measurements of systolic and diastolic function. Cardiac remodeling in CKD may be influenced by treatment modalities, demographics, comorbidities and renal pathology. (J Cardiac Fail 2022;00:1–13)

Keywords: MeSH termsalbuminuria, chronic kidney disease, Cardio-Renal Syndrome, Echocardiography, Hypertrophy, left ventricular, dysfunction, left ventricular.
Background

Death from cardiovascular causes is 2-10 times more likely amongst patients with chronic kidney disease (CKD) as compared with the general population.\textsuperscript{1} Heart failure and ischemic heart disease (IHD) are more frequent among individuals with CKD than without CKD\textsuperscript{1} and presumably preceded by subtle changes in cardiac structure and function. Echocardiography allows for simple, noninvasive evaluation of both; advanced echocardiography – such as speckle tracking – has been proven useful for assessment of subtle abnormalities of prognostic importance.\textsuperscript{2}

Several studies have previously assessed echocardiographic parameters in CKD patients, but findings vary.\textsuperscript{3–5} For example, the prevalence of left ventricle (LV) hypertrophy in CKD patients has been reported to range between 20% to 75%.\textsuperscript{6} Some of the frequently cited data date back decades.\textsuperscript{7,8} Since then, treatment of non-communicable diseases has advanced in Western countries,\textsuperscript{9} likely influencing prevalence of cardiac remodeling in CKD patients. The effect of albuminuria on echocardiographic parameters is seemingly more pronounced than that of estimated glomerular filtration rate (eGFR), but few studies have addressed this topic.\textsuperscript{10} Diastolic dysfunction and impaired global longitudinal strain (GLS) have been reported in CKD patients,\textsuperscript{11,12} but most studies were relatively small and did not adjust for confounders. While heart failure is frequent in end-stage kidney disease,\textsuperscript{13} it is still unclear if eGFR is independently linked to systolic function.\textsuperscript{1,10,14}

We sought to estimate the prevalence of abnormal cardiac structure and function across CKD stages in non-dialysis-dependent patients and to evaluate differences as compared with healthy controls while taking into account clinical and demographic factors. Furthermore, we wanted to investigate the influence of eGFR and albuminuria on echocardiographic measures of cardiac structure and function.

Methods

Population

The CPH-CKD ECHO study is a two-center prospective cohort study. Outpatients were included consecutively from September 2015 through August 2018 at the Departments of Nephrology (RH-CKD cohort), Rigshospitalet and Herlev-Gentofte Hospital (HGH-CKD cohort), Capital Region of Denmark. Inclusion criteria were: CKD, eGFR stages G1 to G5 pre-dialysis, age 30 to 75 yrs. Exclusion criteria for the ECHO sub-study were previous renal transplantation with a functioning graft, pregnancy, intellectual disability, dementia or psychosis, active malignant disease, retracted informed consent, not willing to attend to all required examinations. The control population was enrolled from February through November 2017.\textsuperscript{15} Controls were matched by age-group (5-yr intervals) and by gender distribution to already included patients and included if free of CKD and other known chronic diseases.

Examinations

Clinical examinations. Details have been published previously.\textsuperscript{16} In brief, after informed consent, baseline data were obtained by interview and review of hospital medical files, including data on symptoms and signs of heart disease, renal pathophysiology and co-morbidities. Participants provided venous blood-samples and urine samples, which were analyzed and stored in a biobank. We calculated creatinine-based eGFR using the CKD-EPI formula\textsuperscript{17} and urine albumin to creatinine ratio (UACR). Definition and staging of hypertension and CKD followed the KDIGO 2012 guidelines.\textsuperscript{18}

Echocardiography. A GE VividE9 ultrasound machine (GE Healthcare, Horten, Norway) was used to perform all echocardiograms. All participants were examined with 2-dimensional (2D) echocardiography, color tissue Doppler imaging (TDI) and 2D-speckle tracking in the left lateral decubitus position. Three cardiac cycles were acquired for all projections.

All analyzes were performed by one investigator who was blinded to all other information, including whether the echocardiogram belonged to a patient or a control. Analyzes were performed using EchoPac v. 202 (GE Healthcare, Horten, Norway).

LVEF was determined using the Simpsons biplane method.\textsuperscript{19} Speckle tracking was performed by placing three samples after which a region of interest was defined in all three apical views of the LV. GLS was calculated as the mean of all segments. GLS was infeasible in 68 patients (8%) and 6 controls (4%). Impaired GLS was defined as GLS \(>18\%\).\textsuperscript{19} LV systolic dysfunction was defined as LVEF below 52 % for men or below 54 % for women.\textsuperscript{19} LV dimensions were measured in 2D still frames at end-diastole, and LV mass was calculated using the ASE formula.\textsuperscript{19} Both LV mass and volumes as well as atrial volume were indexed to body surface area (BSA) calculated by the formula of DuBois. We defined LV hypertrophy as left ventricular mass index (LVMI) \(\geq 95 \text{g/m}^2\) for women and \(\geq 115 \text{g/m}^2\) for men and chamber dilatation as indexed left ventricular internal diameter at end diastole (LVIDD) \(\geq 3.2 \text{cm/m}^2\) for women and \(\geq 3.1 \text{cm/m}^2\) for men in accordance to reference values published in 2016 by the ASE/EACVI.\textsuperscript{19}

Diastolic dysfunction. Diastolic dysfunction (DDF) was defined and graded according to the algorithms published in 2016 by the ASE/EACVI.\textsuperscript{20} In
patients with either indeterminable DDF or DDF grade according to the algorithms above, additional grading was performed using available data. Isolated elevation of mitral ratio of peak early to late diastolic filling velocity (E/A ratio) > 2 was interpreted as grade III DDF (except in participants who reported >2 hrs of high intensity physical activity pr. week), and ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e’) > 14 or E/e’ > 9 combined with indexed left atrium volume > 34 ml/m2 were interpreted as grade II DDF.21,22

In patients with atrial fibrillation and reduced EF, mitral deceleration time < 160 ms, elevated tricuspid regurgitation peak velocity in absence of chronic pulmonary disease, and/or E/e’ >= 11 were considered compatible with elevated filling pressures and thus grade II diastolic dysfunction, while atrial size was ignored.20 Patients with either reduced LVEF, LV hypertrophy or LV dilatation without signs of elevated filling pressure were graded as having grade I DDF or - if diastolic data was missing or inconsistent with either grade - were graded as having DDF of indeterminable grade.

Statistics

For tabulation and graphing of results, patients were stratified into three groups according to eGFR categories (G1-G5)18 as determined by eGFR at baseline: G1 and G2 (eGFR > 60 mL/min/1.73 m2), G3 (eGFR 30 to 60 mL/min/1.73 m2), G4 and G5 (eGFR <30 mL/min/1.73 m2). Furthermore, patients were stratified into three albuminuria categories: A1 (<30 mg/g), A2 (30-300 mg/g) and A3 (>300 mg/g).18 However, in statistical analysis, eGFR and UACR were included as continuous variables.

Continuous variables were compared between groups using 2-sided t-test or ANOVA if normally distributed. For skewed distributions, the Wilcoxon rank sum test or the Kruskal-Wallis test was used. Categorical variables were compared using Pearson’s Chi-squared test. Normal distribution was assessed using quantile plots and histograms.

We used uni- and multivariable linear regression (complete case analysis) to evaluate linear associations between continuous variables and eGFR and UACR. Normal distribution of residuals and heteroscedasticity were assessed by plotting of residuals. Variables were transformed with the natural logarithm (ln) if deemed necessary. We assessed collinearity by examining the variance inflation factor and the correlation matrix of predictors. Non-linear associations were evaluated by inspecting restricted cubic spline graphs with three knot values based on Harrel’s recommended percentiles. Three knots were chosen because more knots either did not improve Aikaike’s information criterion or resulted in overfitting on visual inspection of graphs. We used Wald tests to test if the coefficients for splined predictors were zero as a test for overall trend. Uni- and multivariable logistic regression was used to evaluate associations between binary dependent variables and eGFR and UACR. Sensitivity analyses were performed by repeating uni- and multivariable analyses excluding patients with known heart failure, IHD or peripheral arterial disease. A p-value of <0.01 was considered statistically significant. All statistical analysis was performed using STATA v14.2 for Windows.

Ethics

This study was conducted in accordance with the Helsinki Declaration and approved by the Regional Committee on Health Research Ethics of the Capital Region of Denmark (H-3-2011-069) and the Danish Data Protection Agency (30-0840). All participants signed informed consent.

Results

In total, 998 outpatients were included, of which 173 refused to participate in echocardiography, leaving 825 patients. 175 control participants were enrolled resulting in a total number of 1000 participants. For further information, see flow chart (Fig. 1).

Demographics and clinical data

Sixty-two percent of all participants were men. Mean age for patients was 58 yrs (SD 13 yrs.) and 59 yrs (SD 12 yrs) for controls (p=0.17). Controls were less frequently smokers and had a lower BMI than patients. Mean eGFR in patients was 46.7 ml/min/1.73 m2, and median UACR was 131 mg/g. The most frequent CKD etiology was chronic glomerulonephritis or vasculitis (30.2%); CKD in diabetes amounted to 10.9%, hypertensive nephropathy to 5.2%. Prevalence of diabetes mellitus in patients was 20.7% and 84% had hypertension. Thirteen percent of patients had either IHD, heart failure or peripheral arterial disease. Patients at higher stages of CKD were older and more frequently obese. For further details see Table 1.

Cardiac structure

Overall, prevalence of hypertrophy in patients was 9.3%. Patients at stages G4 and G5 had a roughly 5-6 fold increased prevalence of hypertrophy compared with patients at stage G1 and G2, who had similar prevalence of hypertrophy relative to controls (Table 2). In patients with CKD at stage G3 to G5, eccentric hypertrophy was slightly more prevalent.
than concentric (Fig. 2), but the difference was not statistically significant (p-value=0.16).

In patients vs. controls, LV end-diastolic volume were decreased, while septal wall thickness (IVSd), posterior wall thickness (LVPWd) and LVMi were increased independently of confounders (Table 2). IVSd, LVPWd, LVMi increased inversely across eGFR categories (Table 2, Fig. 3). Likewise, linear associations between eGFR and these variables were highly significant in simple, but not in multivariable analysis, which included ln(UACR) (Table 2, Fig. 3). Restricted cubic splines suggested no association between eGFR > 60 ml/min/1.73 m² and LVMI and a weak, independent association between increasing LVMI and declining eGFR below 60 ml/min/1.73 m². However, there was no significant non-linearity, and overall trend was non-significant (Fig. 4). Conversely, all three measures remained linearly and independently associated with ln(UACR) (Table 3, Figs. 3 and 4). Accordingly, ln(UACR) was independently associated with increased risk of hypertrophy (Table 3).

LV end diastolic and systolic volumes showed a quadratic relationship to eGFR (p-value for quadratic coefficient 0.001 and 0.0002, respectively) and tended to be higher at high and low eGFR values (Fig. 6).

Manifest LV dilatation was as uncommon in patients as in controls. Left atrial end systolic volume (LAESVi) increased weakly with decreasing eGFR and increasing UACR, but was only independently associated to UACR (Tables 2 and 3).

Left ventricle – functional measures

All functional measures of LV function were worse in patients than in matched controls. After multivariable adjustment, LVEF and absolute values of GLS remained lower, and occurrence of LV systolic dysfunction higher in patients than in matched controls (Table 2).

In patients, all functional measures were negatively associated with eGFR. However, only GLS was independently associated with eGFR (Table 2). An impaired GLS was present in half of patients in eGFR category G4 and G5 vs. in one third of patients in eGFR category G1 and G2 (Table 2). Moreover, GLS was lower in patients with eGFR < 60 ml/min/1.73 m² vs. patients with higher eGFR, but remained similar in patients with eGFR < 30 ml/min/1.73 m² (Fig. 3). However, observed mean differences between lowest and highest eGFR categories were small, and trends towards systolic dysfunction and impaired GLS with decreasing eGFR did not reach statistical significance (Table 2). UACR was also associated with GLS in simple analysis, but the association was attenuated after adjustment (Table 3).
Table 1. Demographic and clinical data for patients, controls and patients categorized by eGFR category.

|                          | Patients | Controls | p-value | G1 and G2 eGFR
|--------------------------|----------|----------|---------|-----------------|
|                          |          |          |         | > 60 mL/min/1.73 m² |
|                          |          |          |         | G3 eGFR 30 to 60 mL/min/1.73 m² |
|                          |          |          |         | G4 and G5 eGFR
|                          |          |          |         | <30 mL/min/1.73 m² |
|                          |          |          |         | p-value |
| Age, Years               | 825      | 175      | NA      | 212            | 385            | 228 | <0.001 |
| Obesity, by BMI          |          |          | NA      |                |                |     |     |
| Male Gender              | 517      | 107      | NA      | 128 (60.4%)    | 243 (62.1%)    | 146 | 0.60 |
| Systolic BP, mmHg        | 132.0 (17.5) | 130.0 (16.9) | 0.2 | 128.0 (14.9) | 132.6 (17.8) | 134.6 (18.7) | 0.3* |
| Diastolic BP, mmHg       | 81.1 (10.9) | 81.7 (8.9) | 0.5 | 83.2 (10.2) | 81.4 (11.0) | 78.7 (10.9) | 0.03* |
| Heart rate, bpm          | 72.6 (13.1) | 70.1 (11.3) | 0.02 | 73.9 (12.5) | 72.3 (13.2) | 71.9 (13.4) | 0.2* |
| Hypertension             | 696 (84.4%) | 53 (30.3%) | 0.02 | 155 (73.1%) | 343 (89.1%) | 198 (86.8%) | <0.001* |
| Smoking status           |          |          | NA      |                |                |     |     |
| Never                    | 335 (40.7%) | 88 (50.3%) | 90 (42.7%) | 153 (29.7%) | 92 (40.5%) |     |     |
| Active                   | 147 (17.9%) | 18 (10.3%) | 41 (19.4%) | 71 (18.4%) | 35 (15.4%) |     |     |
| Former                   | 341 (41.4%) | 69 (39.4%) | 80 (37.9%) | 161 (41.8%) | 100 (44.1%) |     |     |
| BMI, kg/m²               | 28.5 (5.9) | 25.3 (3.3) | 0.001 | 27.6 (5.7) | 28.6 (5.7) | 29.1 (6.2) | 0.2* |
| Overweight               | 292 (35.4%) | 69 (39.4%) | 65 (30.7%) | 150 (39.1%) | 77 (33.8%) |     |     |
| Obese                    | 278 (33.7%) | 14 (8.0%) | 61 (28.8%) | 131 (34.1%) | 86 (37.7%) |     |     |
| Total cholesterol, mmol/L | 5.1 (1.3) | 5.6 (1.0) | 0.001 | 5.3 (1.2) | 5.2 (1.3) | 4.9 (1.2) | 0.02* |
| eGFR, mL/min/1.73 m²     | 46.7 (25.8) | 82.3 (13.3) | 0.001 | 83.1 (16.6) | 42.8 (8.4) | 19.5 (5.9) | <0.001 |
| Albumin/Creatinine ratio, mg/l | 131.0 (22.0, 681.0) | 2.0 (2.0, 4.0) | 0.001 | 65.0 (12.0, 516.0) | 85.0 (17.0, 473.0) | 325.5 (71.0, 1005.0) | <0.001* |
| Diabetes                 | 171 (20.7%) | 0 (0.0%) | 0.001 | 12 (5.7%) | 94 (24.4%) | 65 (28.5%) | <0.001 |
| Antihypertensive treatment | 647 (78.5%) | 3 (1.7%) | 0.001 | 136 (64.2%) | 324 (84.4%) | 187 (82.0%) | <0.001 |
| ACEI/ARB                 | 522 (63.3%) | 2 (1.2%) | 0.001 | 145 (68.4%) | 259 (67.3%) | 118 (51.8%) | <0.001 |
| Beta Blockers            | 266 (32.2%) | 1 (0.6%) | 0.001 | 25 (11.8%) | 141 (36.6%) | 100 (43.9%) | <0.001 |
| Calcium Channel Blockers | 319 (38.7%) | 0 (0.0%) | 0.001 | 43 (20.3%) | 169 (43.9%) | 107 (46.9%) | <0.001 |
| Aldosterone antagonist   | 42 (5.1%) | 0 (0.0%) | 0.002 | 5 (2.4%) | 26 (6.8%) | 11 (4.8%) | 0.064 |
| Diuretics                | 464 (56.2%) | 2 (1.2%) | 0.001 | 67 (31.6%) | 226 (58.7%) | 171 (75.0%) | <0.001 |
| Ischemic heart disease   | 73 (8.8%) | 0 (0.0%) | 0.001 | 9 (4.2%) | 37 (9.6%) | 27 (11.8%) | 0.02 |
| AMI                      | 37 (4.5%) | 0 (0.0%) | 0.004 | 3 (1.4%) | 21 (5.5%) | 13 (5.7%) | 0.04 |
| CABG                     | 28 (3.4%) | 0 (0.0%) | 0.014 | 2 (0.9%) | 14 (3.6%) | 12 (5.3%) | 0.04 |
| Heart failure            | 73 (8.8%) | 0 (0.0%) | 0.001 | 6 (2.8%) | 36 (9.4%) | 31 (13.6%) | <0.001 |
| Atrial fibrillation      | 70 (8.5%) | 0 (0.0%) | 0.001 | 8 (3.8%) | 31 (8.1%) | 31 (13.6%) | <0.001 |
| Cerebrovascular disease  | 82 (9.9%) | 1 (0.6%) | 0.001 | 9 (4.2%) | 44 (11.4%) | 29 (12.7%) | 0.005 |
| Peripheral artery disease| 39 (4.7%) | 0 (0.0%) | 0.003 | 4 (1.9%) | 17 (4.4%) | 18 (7.9%) | 0.01 |

Continuous variables are reported as mean (standard deviation) or median [interquartile range] in case of skewed distribution. Abbreviations: AMI, acute myocardial infarction; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary bypass artery grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; SD, standard deviation.

*Linear trend.

Diastolic dysfunction occurred in approximately half of patients vs. one third of controls and increased across eGFR categories such that frequency was almost doubled in eGFR category G4 and G5 vs. eGFR category G1 and G2. We noted a high prevalence of increased LV filling pressures (DDF grade II and III) at low eGFR categories with a 10-fold increase at stage G4 and G5 vs. stage G1 & G2. Prevalence of DDF showed increase with decreasing eGFR from 120 to 60 mL/min/1.73 m², but further decrease of eGFR was not predictive of greater probability of DDF (Fig. 6). After multivariable adjustment, the associations between eGFR and DDF was attenuated (Table 2). Similarly, UACR was highly associated with DDF in simple analysis, a result which was only borderline significant after multivariable adjustment (Table 3, Fig. 6).

Sensitivity analysis

Overall, excluding patients with known heart failure, IHD and peripheral arterial disease did not markedly change conclusions. The coefficients for LVEF and GLS vs eGFR were diminished, but GLS remained significantly associated with eGFR. The weak association between UACR and LAESVi was attenuated slightly (p=0.011). The statistical significance of differences between patients and controls regarding LVPWd (p=0.02) and hypertrophy (p=0.010) were also slightly attenuated.
Table 2. Echocardiographic parameters in patients vs. controls and patients stratified by eGFR categories.

| Parameters                              | Patients | Controls | p-value | Adjusted p-value | G1 and G2 eGFR > 60 mL/min/1.73 m² | G3 eGFR 30 to 60 mL/min/1.73 m² | G4 and G5 eGFR < 30 mL/min/1.73 m² | p-value for linear trend | p-value for adjusted linear trend** |
|-----------------------------------------|----------|----------|---------|------------------|----------------------------------|-------------------------------|-------------------------------|---------------------------|-----------------------------------|
| N                                       | 825      | 175      |         |                  | 212                              | 385                           | 228                           | 0.7                       | 0.9                               |
| Chamber dimensions                      |          |          |         |                  |                                  |                               |                               | 0.7                       | 0.9                               |
| LVTTDi, cm/m²                           | 2.46 (0.34) | 2.54 (0.27) | 0.005   | 0.4              | 2.48 (0.33)                      | 2.45 (0.34)                   | 2.47 (0.35)                   |                          |                                   |
| LV systolic dysfunction                 |          |          |         |                  |                                  |                               |                               |                          |                                   |
| GLS, %                                  |          |          |         |                  |                                  |                               |                               |                          |                                   |
| GLS < -18%                              |          |          |         |                  |                                  |                               |                               |                          |                                   |
| LV ejection fraction                   | 59.4 [55.2, 62.8] | 60.8 [57.7, 64.1] | <0.001  | 0.002            | 60.8 [57.5, 63.1]               | 59.2 [55.4, 62.9]             | 57.8 [53.2, 61.9]             | <0.001                    | 0.05                              |
| LV posterior wall thickness             |          |          |         |                  |                                  |                               |                               |                          |                                   |
| IQR, interquartile range               |          |          |         |                  |                                  |                               |                               |                          |                                   |
| LAESVi, ml/m²                           | 48.8 [41.9, 57.4] | 54.9 [47.6, 59.7] | <0.001  | <0.001           | 50.7 [43.7, 58.9]               | 47.4 [40.9, 55.3]             | 49.6 [41.6, 59.1]             |                          | 0.1                               |
| LAESVi ≥ 34 ml/m²                        | 25.9 [21.1, 31.5] | 26.2 [22.3, 30.7] | 0.8      | 0.1              | 24.2 [20.6, 30.4]               | 25.8 [21.1, 30.9]             | 27.6 [21.3, 34.7]             | <0.001                    | 0.7                               |
| LV systolic dysfunction                 |          |          |         |                  |                                  |                               |                               |                          |                                   |
| GLS, %                                  |          |          |         |                  |                                  |                               |                               |                          |                                   |
| GLS > -18%                              |          |          |         |                  |                                  |                               |                               |                          |                                   |
| Diastolic dysfunction                   |          |          |         |                  |                                  |                               |                               |                          |                                   |
| Grade I                                 | 361 (44.1%) | 55 (32.0%) |            | 0.001            | 0.2                             | 75 (35.9%)                    | 186 (48.6%)                   | 100 (44.2%)                | 0.08                              |
| Grade III/IV                            | 74 (9.0%) | 3 (1.7%) |            | 0.001            | 0.3                             | 3 (1.4%)                      | 32 (8.4%)                     | 39 (17.3%)                 | <0.001                                           |
| E/e' (average)                          | 7.9 [6.5, 9.9] | 7.0 [5.8, 8.3] | <0.001  | 0.1              | 7.0 [5.9, 8.5]                   | 8.1 [6.7, 10.0]               | 8.7 [7.0, 11.3]               | <0.001                    | 0.4                               |
| Continuous variables are reported as mean (standard deviation) or median [interquartile range] in case of skewed distribution. *Linear trend derived from linear and logistic regression models including the following variables: age, sex, systolic and diastolic blood pressure, heart rate, ever smoker, body mass index, plasma cholesterol, antihypertensive treatment, diabetes mellitus, heart failure and IHD. Abbreviations: eGFR, estimated glomerular filtration rate; E/e’, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; GLS, global longitudinal strain; IQR, interquartile range; LAESVi, left atrium end systolic volume index; In, natural logarithm; LV, left ventricle; LVEDVi, LV end diastolic volume index, LVESVi, LV end systolic volume index; LVEF, LV ejection fraction; LVTTDi, LV internal diastolic diameter index; IVSd, interventricular septum thickness; LVPWd, LV posterior wall thickness, LVMi, left ventricle mass index; SD, standard deviation; UACR, urine albumin creatinine ratio. **Same as *, but additionally adjusted for eGFR and ln(UACR).
The CPH-CKD ECHO study is a large two-center prospective cohort study enrolling 1000 participants: 825 patients at eGFR stages G1-5 with various etiology and 175 age- and sex-matched controls. The baseline data presented in this study provides a comprehensive and detailed assessment of cardiac structure and function, offering possibilities to relate echocardiographic findings to eGFR and albuminuria. Strengths of the study comprise the large number of patients, who were consecutively sampled and examined with contemporary echocardiographic methods by a single observer. Furthermore, echocardiographic analyses were performed blinded.

**Discussion**

The CPH-CKD ECHO study is a large two-center prospective cohort study enrolling 1000 participants: 825 patients at eGFR stages G1-5 with various etiology and 175 age- and sex-matched controls. The baseline data presented in this study provides a comprehensive and detailed assessment of cardiac structure and function, offering possibilities to relate echocardiographic findings to eGFR and albuminuria. Strengths of the study comprise the large number of patients, who were consecutively sampled and examined with contemporary echocardiographic methods by a single observer. Furthermore, echocardiographic analyses were performed blinded.

**Fig. 2.** Left ventricle geometry across groups of participants. Numbers represent percentages within groups.
Abbreviations: CKD, chronic kidney disease. G1+2, eGFR > 60 ml/min/1.73 m²; G3, eGFR 30-60 ml/min/1.73 m²; G4+5, eGFR <30 ml/min/1.73 m²; A1, albuminuria <30 mg/g; A2, albuminuria 30-300 mg/g; A3, albuminuria >300 mg/g.

**Fig. 3.** 3D bar graphs illustrating observed (red) and predicted (blue) mean values for LVMI, LVEF and GLS (in absolute numbers) stratified by eGFR and albuminuria categories. Predictions are adjusted for age, sex, systolic and diastolic blood pressure, heart rate, ever smoker, body mass index, plasma cholesterol, eGFR, ln(UACR), antihypertensive treatment, diabetes mellitus, heart failure and IHD.
Abbreviations: eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; ln, natural logarithm; LVEF, left ventricle ejection fraction; LVMI, left ventricle mass index; UACR, urine albumin creatinine ratio.
eGFR categories: G1+2, > 60 ml/min/1.73 m²; G3, 30-60 ml/min/1.73 m²; G4+5, <30 ml/min/1.73 m²
Albuminuria categories: A1, <30 mg/g; A2, 30-300 mg/g; A3, >300 mg/g.
with respect to clinical status and according to current guidelines.

Patients with CKD demonstrated both increased LV wall thickness and decreased diastolic LV volumes compared with controls, as well as lower LVEF and GLS. These changes were primarily apparent in patients with eGFR < 60 ml/min/1.73 m². Estimated GFR was inversely associated with all functional measures and independently associated with GLS. LV volumes showed a quadratic relationship with eGFR and were lowest in patients at GFR stage G3 (Fig. 5). UACR was inversely associated with functional measurements, except LVEF, especially diastolic dysfunction. Moreover, UACR was independently associated with LV wall thickness, LVMI and LAESVi.

Hypertrophy

In the current cohort, we report the lowest prevalence of hypertrophy in a cohort of patients with CKD to date ranging from 2.4% at stage G1 and G2 to 14.0% at stage G4 and G5.

Other studies have reported prevalence of hypertrophy in patients with CKD ranging from 23% to 74%. However, differences in ethnic composition, demographic variables and comorbidities might explain the observed disparity. For example, the CRIC cohort participants featured higher prevalence of obesity (55% vs. 34%), IHD (22% vs. 8.8%) and 54% were Non-Caucasians, primarily Afro-Americans, who have higher propensity to LV hypertrophy. Paoletti et al – who reported particularly high prevalence of LV hypertrophy – included mostly older participants, many of them with long-standing hypertension.

A further explanation might be the advancement in treatment of lifestyle diseases in Western countries over the recent years, which has brought about a drastic decline in related morbidity. This includes diabetic nephropathy, which was more prevalent in US and Asian CKD cohorts than in our study and is particularly associated with increased LV mass. Finally, measurement results regarding LV mass vary depending on echocardiographic methods. However, the methods used in the present study (harmonic imaging, 2D linear measurements) are thought to result in overestimation rather than underestimation of LV mass and cutoffs for LV hypertrophy employed in the present study are equally or more stringent than in previous studies. In summary, the above findings indicate, that prevalence and grade of hypertrophy in patients with CKD are influenced by ethnic and demographic factors, comorbidities, treatment and renal pathophysiology and might be lower than previously suspected in certain populations.

Despite the low prevalence of LV hypertrophy in our cohort, previous findings which linked increasing LV mass and LV hypertrophy to progressive renal insufficiency are confirmed with some variations. Previous studies have reported eGFR stages G3b-5 to be the most associated with LVH, which matches our findings. However, while stage G3 had significantly higher LVMI than lower stages, the differences were negligible when compared with higher
stages. This is supported by longitudinal follow-up in the CRIC cohort, where LV mass in patients with eGFR stage G3 who had progressed to end-stage kidney disease had remained largely unaltered. As of now, it is uncertain how much these observations are biased by increased mortality in those CKD patients, who do suffer increase in LV mass as kidney disease progresses (survival bias).

We found that LV wall thickness and LV hypertrophy was independently associated with UACR. This is in agreement with results from ARIC, JAC-CKD and Paolletti et al. An independent association between LVMI and eGFR as seen in previous studies could not be confirmed. This might be due to sample size, low prevalence of hypertrophy and use of creatinine-based eGFR. However, results from ARIC, where both creatinine and cystatin-C were used to calculate eGFR, confirmed a monotone relationship between ln(UACR) and LVMI, while only eGFR <45 was associated with greater LV mass. Similar trends were identified in our study, albeit the trend for eGFR was non-significant. A quadratic trend between eGFR and LVEDVi, albeit not mentioned in the text, was apparent in the linear spline models reported by Matsushita et al and is confirmed in the present study (Fig. 5).

Development of hypertrophy in CKD is multifactorial: increased LV wall stress due to hypertension is thought to cause concentric remodeling and reduction of LV volumes, especially in the early phases of CKD. In advanced CKD, anemia and volume overload can lead to increase of LV volumes and, hence eccentric hypertrophy.

In our study, we noted a slightly higher occurrence of eccentric than concentric hypertrophy. Previous findings have been conflicting with some studies reporting highest occurrence of concentric hypertrophy, whereas others primarily reported eccentric hypertrophy. In conclusion, varying degrees of volume overload and anemia in patients with CKD

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**Table 3. Echocardiographic parameters in patients stratified by albuminuria categories (n=796)**

| Chamber dimensions | A1 UACR <30 mg/g | A2 UACR 30-300 mg/g | A3 UACR >300 mg/g | p-value for linear trend | p-value for adjusted linear trend* |
|--------------------|----------------|---------------------|------------------|-------------------------|----------------------------------|
| N                  | 246            | 253                 | 295              |                         |                                  |
| LVDDi, cm/m²       | 2.48 (0.36)    | 2.46 (0.34)         | 2.44 (0.33)      | 0.2                     | 0.7                              |
| Dilated LV         | 8 (3.3%)       | 7 (2.8%)            | 4 (1.4%)         |                         |                                  |
| IVs, cm            | 0.88 (0.19)    | 0.92 (0.19)         | 0.96 (0.21)      | <0.001                 | <0.001                           |
| LVWPd, cm          | 0.87 (0.18)    | 0.91 (0.19)         | 0.95 (0.20)      | <0.001                 | <0.001                           |
| LVMI, g/m²         | 71.6 [61.3, 84.0] | 75.8 [63.0, 89.7]  | 79.5 [66.4, 94.2] | <0.001                 | <0.001                           |
| LV hypertrophy     | 13 (5.3%)      | 21 (8.2%)           | 41 (13.9%)       |                         |                                  |
| LV geometry        |                |                     |                  |                         |                                  |
| Concentric remodeling |              |                     |                  |                         |                                  |
| Hypertrophy        |                |                     |                  |                         |                                  |
| Concentric         | 5 (2.0%)       | 12 (4.7%)           | 17 (5.8%)        | 0.004                   | 0.02                             |
| Eccentric          | 8 (3.3%)       | 9 (3.5%)            | 24 (8.1%)        | <0.001                 | 0.06                             |
| LVEF, %            | 59.5 [55.6, 63.0] | 59.5 [55.1, 63.0]  | 59.0 [54.6, 62.6] | 0.3                     | 0.98                             |
| Systolic dysfunction |                |                     |                  |                         |                                  |
| GLS, %             | 44 (17.9%)     | 41 (16.1%)          | 55 (18.8%)       | 0.03                    | 0.5                              |
| GLS > -18%         | -18.2 (3.1)    | -18.0 (2.6)         | -17.7 (3.0)      | 0.003                   | 0.6                              |
| Diastolic dysfunction | 93 (41.2%)    | 113 (47.9%)         | 135 (50.0%)      | <0.001                 | 0.3                              |
| Grade I            | 93 (38.1%)     | 119 (46.7%)         | 141 (48.6%)      | <0.001                 | 0.1                              |
| Grade II/III       | 20 (8.2%)      | 22 (8.6%)           | 30 (10.3%)       | 0.02                    | 0.3                              |
| E/e (average)      | 7.8 [6.2, 9.4] | 8.0 [6.4, 10.1]     | 7.9 [6.7, 10.2]  | 0.01                   | 0.1                              |

Continuous variables are reported as mean (standard deviation) or median [interquartile range] in case of skewed distribution. Abbreviations: E/e, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; IQR, interquartile range; LAESVi, left atrium end systolic volume index; ln, natural logarithm; LV, left ventricle; LVEDVi, LV end diastolic volume index; LVEF, LV ejection fraction; LVMI, LV internal diastolic diameter index; IVs, interventricular septum thickness; LVWPd, LV posterior wall thickness, LVMi, left ventricle mass index; SD, standard deviation; TR, tricuspid regurgitation; UACR, urine albumin creatinine ratio.

*Linear trend derived from linear and logistic regression models including the following variables: age, sex, systolic and diastolic blood pressure, heart rate, ever smoker, body mass index, eGFR, ln(UACR), plasma cholesterol, antihypertensive treatment, diabetes mellitus, heart failure and IHD.
might explain the observed inclinations to eccentric hypertrophy, but concentric remodeling and hypertrophy seem to be most consistently related to albuminuria, which has also been demonstrated in non-CKD hypertensives with low grade albuminuria.29

**Systolic and diastolic function**

Interestingly, the low presence of hypertrophy reported in the present study did not translate into lower prevalence of systolic and diastolic dysfunction. To the contrary, most previous studies have reported slightly better systolic function in patients with CKD with mean LVEF >60% (vs. 59.4 in the present study) and similar or lower prevalence of systolic dysfunction (1.5%-18%).4,14,24 Diastolic dysfunction is defined differently between studies. The CASCADE study reported similar prevalence for DDF using guidelines published in 2009 for grading of diastolic function.4 In contrast, occurrence of DDF in CRIC participants was somewhat higher (71% vs. 55% in our study) – here definition of DDF was
based solely on early and late mitral inflow parameters. Some studies reported worse diastolic, but not systolic, function in patients with CKD vs. healthy controls in unadjusted comparison. We found both diastolic and systolic function to be impaired, but after multivariable adjustment, LVEF and GLS rather than diastolic function remained significantly worsened in patients with CKD vs. healthy controls.

Previous studies reported impaired GLS but preserved LVEF at less advanced stages of CKD. At later stages, longitudinal findings in the CRIC cohort and from the CASCADE study showed that mean LVEF had deteriorated between eGFR stages G3 and G5. The proposed pathways for these functional deteriorations include LV hypertrophy causing DDF due to increased wall stiffness in early stages of CKD and subendocardial fibrosis and ischemia at later stages, thus leading to structural disruptions and systolic dysfunction. As eGFR falls below 30 ml/min/1.73 m², accumulation of uremic toxins is thought to further reduce the contractile function of the myocardium. However, we witnessed in this cohort seemingly simultaneously decreased parameters of both systolic and diastolic function in patients with eGFR below 60 ml/min/1.73 m², accompanied by increased prevalence of hypertrophy. Earlier stages of CKD had similar functional parameters and prevalence of hypertrophy compared with healthy controls.

Contrary to previous studies, we find no independent association between albuminuria and functional cardiac parameters, albeit UACR was borderline associated with diastolic dysfunction. Notably, Katz et al found UACR to be associated with e/E in participants of the HYPERgen study, but not in participants without LV hypertrophy. Thus, the low prevalence of hypertrophy in the current study might influence our findings. Furthermore, the mean eGFR in participants of the HYPERgen study was ≥ 80 ml/min/1.73 m², even in the highest quartile of UACR. Hence, results from this study cannot readily be extrapolated to our CKD cohort. Finally, albuminuria in individuals with hypertension or diabetes could indicate systemic end-organ damage due to long-standing disease or poorly controlled disease status and may therefore be closer associated with deterioration in cardiac function than albuminuria due to other causes, i.e. nephritis.

Limitations

Our findings are limited by the cross-sectional design of the present study and need to be confirmed by longitudinal follow-up. Racial and socioeconomic properties of the cohort may limit generalizability of findings to other populations. We did not collect data on duration of comorbidities. We used consecutive sampling of participants to minimize selection bias, but residual bias cannot be ruled out due to non-random sampling.

Conclusion

In this cohort of patients with CKD, we report lower prevalence of hypertrophy than previous studies. Cardiac remodeling in CKD may be influenced by treatment modalities, demographics, comorbidities and renal pathology. Subclinical decrease of LV systolic function, primarily decreased longitudinal function, seems to occur primarily between early and moderately advanced stages in CKD, alongside increase in LV mass and diastolic dysfunction. However, only longitudinal follow-up can finally establish a timeline of changes in LV structure and function during the course of CKD. The observed changes in LVEF and GLS are small – future studies are required to relate them to clinical symptoms and cardiovascular outcomes.

Lay summary

- Patients with low levels of chronic kidney disease have hearts that are similar to healthy individuals. But in patients with moderate disease, the heart’s volume is already decreased, the heart’s walls are thickened, the heart is stiffer and pumps blood slightly less effective.
- However, we find that patients with chronic kidney disease might have less thickened hearts than previously reported. This might depend on the cause of their kidney disease, if they suffer from other diseases and how they are treated.
- The amount of protein leakage in the urine seems closely associated to the heart’s wall thickness.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.09.002.
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