

Left Ventricular Structure in Patients With Mild-to-Moderate CKD—a Magnetic Resonance Imaging Study



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Introduction: The high burden of left ventricular (LV) abnormalities in patients with advanced chronic kidney disease (CKD) is well established. However, less is known about the prevalence, patterns, and determinants of LV abnormalities in patients with early CKD.

Methods: We examined LV structure in 290 patients with a median estimated glomerular filtration rate (eGFR) of 51 ml/min per 1.73 m² by magnetic resonance imaging (MRI). We explored associations with clinical and hemodynamic parameters, hydration (bioimpedance), endothelial function, inflammation (including C-reactive protein and tumor necrosis factor- α and its soluble receptors) and mineral bone disease (MBD) markers (including vitamin D, parathyroid hormone, α -klotho and fibroblast growth factor-23).

Results: Normal geometry was found in 56% of patients, dilation in 4%, concentric remodeling in 10%, and LV hypertrophy in 29%. Linear regression analysis revealed that greater LV mass was independently associated with male sex, greater body mass index (BMI), and higher 24-hour systolic blood pressure (24-hour SBP). Concentric remodeling was independently associated with age, male sex, higher 24-hour SBP, and greater hemoglobin levels. Surprisingly, neither hydration status, nor endothelial function, nor any of the inflammatory or MBD parameters added significantly to these models.

Conclusion: Abnormal LV structure was found in almost one-half of the patients. Reducing BMI and 24-hour SBP and avoiding high hemoglobin concentrations appear to be the key factors to prevent abnormal LV remodeling in patients with mild-to-moderate CKD.

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KEY WORDS: chronic kidney disease; hypertension; kidney diseases; left ventricular hypertrophy; mineral metabolism
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The high burden of abnormal left ventricular (LV) structure in patients with advanced chronic kidney disease (CKD) is well established. CKD patients

with LV hypertrophy (LVH) have an increased risk of cardiovascular (CV) events^{1,2} and, specifically, an increased risk of sudden cardiac death.³ There is also evidence that concentric remodeling of the LV, even in the absence of frank hypertrophy, may increase CV risk.⁴ Thus, abnormal LV structure has been suggested as a therapeutic target,⁵ but the pathogenesis of CKD-related LV abnormalities remains poorly understood.

In addition to the “classic” risk factors such as increased blood pressure (BP), “nonclassic” factors

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such as anemia,⁶ overhydration⁷, endothelial dysfunction,⁸ and mineral bone disease (MBD)—related mechanisms have been implicated. With regard to MBD, low vitamin D,⁹ elevated parathyroid hormone (PTH),¹⁰ and, more recently, elevated fibroblast growth factor (FGF)—23¹¹ have been proposed as contributing factors. However, previous studies have focused on patients with advanced CKD, and have almost exclusively been performed with echocardiography. A much more precise assessment is possible using cardiac magnetic resonance imaging (MRI).¹²

To this end, we examined 290 patients with mild-to-moderate CKD who were enrolled in the CARdioVascular In-Depth Assessment in Chronic Kidney Disease (CARVIDA) study, a substudy of the German Chronic Kidney Disease (GCKD) study, and assessed LV structure by MRI together with a comprehensive assessment of classic and nonclassic risk factors of CKD-LVH.

MATERIALS AND METHODS

Study Design and Population

The CARVIDA study was planned and carried out as a substudy of the GCKD study. The study design of GCKD has been reported in detail.^{13,14} In brief, 5127 Caucasian CKD patients 18 to 74 years of age were included if they met 2 inclusion criteria: an estimated glomerular filtration rate (eGFR) of 30 to 60 ml/min per 1.73 m² or manifest proteinuria (>500 mg/d or equivalent) in case the eGFR was >60 ml/min per 1.73 m². The GCKD study has been reviewed and approved by local ethics committees and entered into the national registry for clinical studies (DRKS 00003971). The CARVIDA study enrolled a total of 322 patients at the study centers Würzburg, Aachen, and Erlangen, which are 3 of 9 regional GCKD centers in Germany.

Cardiac MRI

Magnetic resonance imaging was carried out on 1.5-Tesla scanners featuring high-performance gradients (Magnetom Aera or Magnetom Avanto, Siemens AG, Erlangen, Germany). The imaging protocol contained balanced steady-state free precession (bSSFP) cine sequences for functional and volumetric analysis. Retrospectively gated electrocardiographically triggered bSSFP cine images were acquired while patients were holding their breath in standard 4-chamber, 3-chamber, and 2-chamber long- as well as short-axis views of the entire left ventricle. The following scan parameters were used: slice thickness 8 mm, in-plane resolution 2.5 × 1.8 mm, time to echo (TE) 1.1 millisecond, time to repetition (TR) 42 milliseconds, and flip angle 50°. Some participants could not undergo or finish the MRI measurements because of anxiety.

Data were complete in 290 patients, which form the basis for the current analysis.

Office and Ambulatory BP Measurements and Ambulatory Pulse Wave Analysis

Office BP was recorded as the mean of 3 oscillometric measurements in the supine position after 5 minutes of rest. Twenty-four-hour ambulatory BP measurement (ABPM) was performed with the Mobil-O-Graph PWA monitor (IEM Healthcare, Stolberg, Germany). This device allows concurrent assessment of ambulatory parameters of arterial wave reflection (central augmentation index) and stiffness (pulse wave velocity) by construction of the central pulse wave via an inbuilt algorithm (ARCSolver). Central augmentation index is defined as the ratio of the augmentation pressure (difference between the first and the second peak of the central BP wave) to pulse pressure (difference between systolic and the diastolic pressure readings) given as a percentage. Pulse wave velocity is calculated after signal processing from the time difference between the estimated forward and reflected waves.

Body Composition Measurements

Fluid status was measured with a portable whole-body bioimpedance spectroscopy device (body composition monitor, Fresenius Medical Care, Bad Homburg, Germany). Fluid status is represented as “overhydration” (OH, expressed in liters), based on a 3-compartment model developed by Chamney *et al.*¹⁵ The 3 compartments are lean tissue mass, adipose tissue mass, and OH. Overhydration is the difference between the amount of extracellular water in the tissue actually detected by the body composition monitor and the amount of tissue water predicted using physiological models under euvoletic conditions. As such, negative values of OH represent hypovolemia, whereas positive values indicate hypervolemia.

Flow-Mediated Vasodilation

Flow-mediated vasodilation of the brachial artery was determined according to the consensus of the International Brachial Artery Reactivity Task Force with a linear ultrasound probe with 10 MHz.¹⁶ Image analysis was performed off-line with the U.S. Food and Drug Administration—approved software Brachial Analyzer (Medical Imaging Applications LCC, Carolville, IA).

Measurements of Clinical Chemistry, Markers of Inflammation, and MBD Parameters

Creatinine was analyzed using an isotope dilution mass spectrometry-traceable methodology, and eGFR values determined with the Chronic Kidney Disease—Epidemiology Collaboration (CKD-EPI) formula.¹⁷ Interleukin-6 (IL-6) was measured using a

chemiluminescent immunometric assay (Cobas, Roche Diagnostics, Penzberg, Germany). The 116 (36.5%) IL-6 measurements that were below the lower limit of detection (LOD) were transformed as $\text{LOD}/\sqrt{2}$ before further analysis. High-sensitivity C-reactive protein was measured using the Dimension Vista 500 analytical system (Siemens AG, Erlangen, Germany). Human tumor necrosis factor (TNF)- α was measured with enzyme-linked immunosorbent assay (ELISA; R&D Systems, Wiesbaden, Germany). Because 279 of the measurements (97.2%) were below the lower LOD, TNF- α was used as a dichotomized variable in the analyses (not detected or detected). Human soluble TNF receptor I (sTNF-RI) was measured with an enzyme-linked immunoassay (EIA; EKF Diagnostics, Barleben, Germany). Human soluble TNF receptor II (sTNF-RII) was measured with ELISA (R&D Systems). The C-terminal peptide of FGF-23 (i.e., the assay captures the intact FGF-23 and the C-terminal peptide of FGF-23) was measured with ELISA (Biomedica, Vienna, Austria). For the 15 (4.7%) measurements that were above the upper LOD, the value of the upper LOD was used for further analysis (10 pmol/l). Intact FGF-23 was measured with ELISA (Kainos Laboratories, Tokyo, Japan). For the 4 measurements (1.3%) that were above the upper LOD, the value of the upper LOD was used for further analysis (500 pg/ml). Human soluble α -Klotho was determined by ELISA (IBL, Gunma, Japan). 1,25-OH vitamin D and intact PTH were measured on the IDS-iSYS Automated System (Immunodiagnostic Systems, Frankfurt am Main, Germany). Intra- and interassay precision were <10% for all the above measurements.

Data Analysis

Statistical analyses were performed with IBM SPSS Statistics Version 24 (IBM SPSS, Armonk, NY). Graphs were generated with GraphPad Prism 6 (GraphPad Software, San Diego, CA). Normal distribution was assessed by the Kolmogorov–Smirnov test. Data are presented as mean with SD for normally distributed variables, medians with interquartile range for non–normally distributed variables, and frequencies (percentages) for categorical variables. Correlation was assessed by calculating the Pearson (r) and Spearman (ρ) correlation coefficients as appropriate. It should be noted that the correlation analyses were performed merely in an exploratory fashion. To take into account the interrelation of some LV parameter, we performed partial correlation analyses to study the relationship between clinical parameters and LV parameters. Linear regression analyses were performed to study the effects of variables suggested to be potentially relevant by these partial correlation analyses on end-diastolic volume (EDV), left ventricular mass (LVM), and concentricity. Left ventricular parameters were not normally

Table 1. Clinical characteristics of study patients (N = 290)

Parameter	Value
Demographics	
Age, yr	61 (53–71)
Gender, male/female	175/115
Weight, kg	83 \pm 16
Height, cm	172 \pm 9
Body mass index, kg/m ²	27 (25–31)
Overhydration, L	0.1 (–0.8 to –0.7)
Never/former/current smoker, n (%)	123 (43)/126 (44)/40 (14)
Comorbidities	
Hypertension, n (%)	271 (93)
Hypertension duration, yr	14 (7–22)
Diabetes mellitus, n (%)	67 (23)
Coronary artery disease, n (%)	29 (10)
Cerebrovascular disease, n (%)	22 (8)
Peripheral vascular disease, n (%)	11 (4)
Cause of renal disease	
Primary glomerulopathy, n (%)	107 (37)
Vascular nephropathy, n (%)	75 (26)
Diabetic nephropathy, n (%)	46 (16)
Systemic disease affecting the kidney, n (%)	40 (14)
Interstitial nephropathy, n (%)	25 (9)
Hereditary nephropathy, n (%)	16 (6)
Renal parameters and hemoglobin	
Serum creatinine, $\mu\text{mol/l}$	124 (104–159)
eGFR (ml/min per 1.73 m ²)	51 (41–62)
UACR, mg/g creatinine	63 (8–375)
Hemoglobin, g/dl	13.7 (12.6–14.7)

eGFR, estimated glomerular filtration rate; UACR, urinary albumin excretion rate.

distributed and were therefore logarithmically transformed for correlation and linear regression analyses.

RESULTS

Clinical Characteristics

The clinical characteristics of the study sample are shown in Table 1. Overhydration ranged from values of –9 L (indicating hypovolemia) to +11 L (indicating hypervolemia). More than 90% of patients had a diagnosis of arterial hypertension, and almost one-fourth of patients had type 2 diabetes mellitus. Common causes of the patients' renal disease according to their nephrologists were primary glomerulopathy, vascular nephropathy, diabetic nephropathy, or a systemic or rheumatologic illness. The eGFR was mildly to moderately reduced, consistent with study inclusion criteria.¹³ In line with the different etiologies of CKD, we observed a wide range in the level of albuminuria. Hemoglobin also varied widely; 31% of men had a hemoglobin <13.5 g/dl, and 35% of women a hemoglobin <12.5 g/dl. Clinical characteristics of the patients included in this phenotyping substudy were very similar to those of the parent GCKD study.¹⁴

Left Ventricular Structure as Determined by MRI

Data on LV structure and function are presented in Table 2. With regard to discrete parameters, we applied

Table 2. Left ventricular parameters by magnetic resonance imaging (N = 290)

Continuous parameters	Median (range)
EDV, ml	132 (109–156)
EDVI, ml/m ²	68 (58–77)
ESV, ml	51 (40–66)
ESVI, ml/m ²	26 (21–32)
SV, ml	80 ± 18
SVI, ml/m ²	41 (35–47)
EF, %	61 (56–64)
LVM, g	124 (102–147)
LVMi-BSA, g/m ²	63 (54–71)
LVMi-height, g/m ²	72 (61–82)
LVMi-height ^{2.7} , g/m ²	28 (25–33)
Concentricity (LVM/EDV)	0.93 (0.80–1.09)
Discrete parameters	n (%)
Normal LV geometry	163 (56.4)
Normal LV geometry and function	158 (54.7)
LVH	85 (29.4)
LVH, concentric	42 (14.5)
LVH, eccentric (i.e., with dilation)	16 (5.5)
LV dilation (with and w/o LVH)	27 (9.3)
LV dilation (w/o LVH)	11 (3.8)
Concentric remodeling (with and w/o LVH)	72 (24.9)
Concentric remodeling (w/o LVH)	30 (10.4)
Systolic dysfunction (EF < 50%)	21 (7.2)

BSA, body surface area; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; ESV, end-systolic volume; ESVI, end-systolic volume index; LV, left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; SV, stroke volume; SVI, stroke volume index; w/o, without.

the sex-specific cut-off values (>95th percentile) published by the Framingham Offspring Study for the definition of LVH, LV dilation, and concentric remodeling.¹⁸ Concentric LVH was defined as LVH in the presence of increased concentricity (>95th percentile). Eccentric LVH was defined as LVH in the presence of increased end-diastolic volume index (>95th percentile). **Figure 1** shows the distribution of normal cardiac geometry, LV dilation without LVH, concentric remodeling without LVH, and LVH (concentric and eccentric) in the whole patient sample and separately in men and women. Overall, normal LV geometry was found only in 56.4% of the patients. Of note, abnormal LV structure was more prevalent in women than in men with CKD (*P* = 0.06 by χ^2 test) (**Figure 1**).

Office BP, Ambulatory BP, and Ambulatory Pulse Wave Analysis

Results of office and ambulatory BP measurements and ambulatory pulse wave analysis are shown in **Table 3**. Office systolic BP was controlled to <140 mm Hg in 70% of patients. A much stricter value of <120 mm Hg, as suggested by the recent Systolic Blood Pressure Intervention Trial (SPRINT),¹⁹ was achieved in only 18% of our patients. Twenty-four-hour SBP was controlled to <130 mm Hg in 65% of the patients. Blood pressure was treated with a median of 2

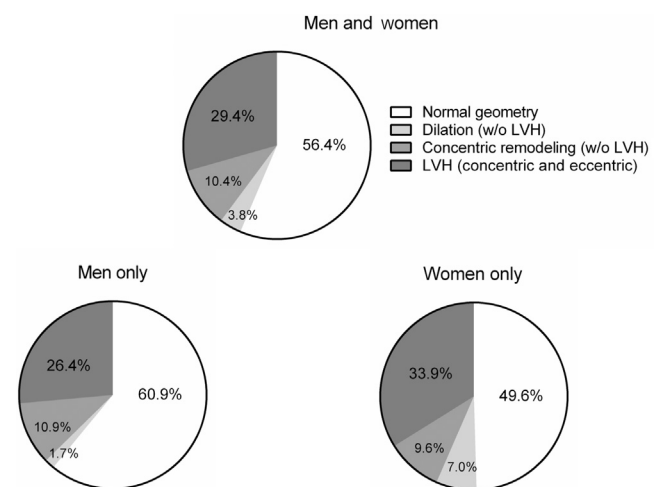


Figure 1. Distribution of left ventricular geometry in the Cardiovascular In-Depth Assessment in Chronic Kidney Disease (CARVIDA) study. LVH, left ventricular hypertrophy; w/o, without.

antihypertensive medications, most commonly angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics and β -blockers.

Endothelial Function, Inflammation, and CKD-MBD Parameters

Results regarding endothelial function, inflammation and MBD parameters are given in **Table 4**. Median dilation of the brachial artery after 3 minutes of forearm ischemia was 3.2%, which is substantially impaired compared with published normal values (>6.0% considered to be normal in subjects ~60 years of age).²⁰ Applying a cut-off value used in clinical

Table 3. Hemodynamic parameters and antihypertensive therapy (N = 290)

Parameter	Value
Office SBP, mm Hg	132 (123–144)
Office DBP, mm Hg	81 (75–90)
24-h SBP, mm Hg	123 (116–132)
24-h DBP, mm Hg	77 (69–82)
24-h PP, mm Hg	47 (42–53)
24-h central SBP, mm Hg	113 ± 11
24-h central DBP, mm Hg	78 ± 10
24-h central to peripheral SBP amplification, mm Hg	10 (8–12)
24-h central Alx, %	25 ± 7
24-h PWV, m/s	9 (8–10)
No. of BP medications	2 (1–3)
ACE inhibitor, n (%)	130 (45)
ARB, n (%)	132 (46)
β -Blocker, n (%)	122 (42)
Calcium channel antagonist, n (%)	103 (36)
Diuretic, n (%)	145 (50)
Thiazide diuretic, n (%)	85 (29)
Loop diuretic, n (%)	71 (25)
MR antagonist, n (%)	18 (6)

ACE, angiotensin-converting enzyme; Alx, augmentation index; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; MR, mineralocorticoid receptor; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

Table 4. Endothelial function, inflammation, and CKD-MBD parameters (N = 290)

Parameter	Value
Endothelial function	
Brachial artery dilation after 90 s, mm	0.13 (−0.01 to −0.28)
Brachial artery dilation after 90 s, %	3.1 (−0.2 to −6.5)
Inflammation	
hs-CRP, mg/l	1.6 (0.8–3.8)
Interleukin-6, pg/ml	2.1 (1.5–3.9)
TNF- α elevated (>1.6 pg/ml), n (%)	8 (2.8)
sTNF-RI, pg/ml	2178 (1666–2860)
sTNF-RII, pg/ml	4623 (3564–6520)
CKD-MBD parameters	
Calcium, mmol/l	2.3 (2.2–2.3)
Phosphate, mmol/l	1.0 (0.9–1.1)
1,25-OH-vitamin D, pg/ml	25 (20–34)
PTH, pg/ml	40 (27–62)
α -klotho, pg/ml	617 (507–742)
FGF-23 intact, pg/ml	70 (51–99)
FGF-23 C-terminal, pmol/l	1.3 (0.9–2.4)

CKD-MBD, chronic kidney disease–mineral bone disease; FGF-23, fibroblast growth factor–23; hs-CRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone; sTNF-R, tumor necrosis factor receptor; TNF, tumor necrosis factor.

routine of 5 mg/l, 52 patients (18%) had elevated high-sensitivity C-reactive protein levels. Applying a cut-off value of 10 pg/ml, only 15 patients (5%) had elevated levels of IL-6. Tumor necrosis factor- α was detectable in only 2.8% of patients. Values of the sTNF-RI and sTNF-RII demonstrated a wide range (no established reference values exist, but median [range] for sTNF-RI in healthy subjects according to the assays' manufacturer are 836 [503–1583] pg/ml; in the case of sTNF-RII, mean value [range] are 1726 [1003–3170] pg/ml). The normal range of 1,25-OH vitamin D according to the assays' manufacturer is 26.1 to 95.0 pg/ml. The median value of of 25 pg/ml in our patients was just below the lower end of that range, and 176 patients (57%) had values lower than the normal range. The reference range for intact PTH is 15 to 65 pg/ml. A total of 79 patients (25%) had elevated levels. Levels of α -klotho, intact FGF-23, and C-terminal FGF-23 varied widely, and no established reference values exist for these novel parameters.

Correlations With LV Parameters

In an exploratory fashion, we performed partial correlation analyses between the available clinical, hemodynamic, endothelial function, inflammation, and MBD parameters with key LV parameters. To adjust for the correlations between ln EDV and ln LVM ($r = 0.557$, $P < 0.001$), and ln EF and ln LVM ($r = -0.208$, $P < 0.001$), the correlation of any clinical parameter with ln EDV was adjusted for correlations of that parameter with ln LVM; similarly, analysis of ln EF was adjusted for ln LVM, and the analysis of LVM was adjusted for ln EDV and ln EF. Only those clinical variables were subsequently included in linear regression analysis of ln EDV, ln LVM, and ln concentricity that showed a significant relationship (Table 5). Of note, from similar parameters with high collinearity (e.g., high-sensitivity C-reactive protein and IL-6), only the variable with the strongest univariate relationship was included into regression analysis. Figure 2 shows the correlation between BMI and LV mass, Figure 3 the correlation between 24-hour SBP and LV mass, and Figure 4 the correlation between hemoglobin and concentricity. Variables not included in regression analyses are given in Supplementary Table S1.

Linear Regression Analyses of ln EDV, ln LVM, and ln Concentricity

Table 6 shows the results of the linear regression analyses. Entering the variables into a linear regression model that showed significant relationships in partial correlation analysis, ln EDV was independently associated with age, BMI, and OH. Age had a negative relationship, and BMI and OH a positive relationship, with ln EDV. The ln LVM was independently associated with sex, BMI, and 24-hour SBP, whereas age, smoking, creatinine, UACR, hemoglobin, sTNF-RI, and PTH did not contribute to the model. Finally, ln concentricity was independently associated with age, sex, 24-hour SBP, and hemoglobin levels, whereas smoking, creatinine, UACR, sTNF-RI, and PTH did not contribute to the model.

Table 5. Correlations of variables included in regression analysis with LV parameters (N = 290)

Parameter	Age	Sex	BMI	Smoking	OH	Creatinine	UACR	Hb	24-h SBP	sTNF-RI	PTH
ln EDV, ml	$r = -0.233$ $P < 0.001$	$r = -0.098$ $P = 0.095$	$r = 0.129$ $P = 0.028$	$r = -0.022$ $P = 0.713$	$r = 0.119$ $P = 0.044$	$r = -0.085$ $P = 0.151$	$r = -0.070$ $P = 0.243$	$r = -0.116$ $P = 0.054$	$r = -0.089$ $P = 0.137$	$r = -0.147$ $P = 0.042$	$r = -0.089$ $P = 0.135$
ln EF, %	$r = -0.031$ $P = 0.595$	$r = 0.151$ $P = 0.010$	$r = 0.023$ $P = 0.702$	$r = 0.015$ $P = 0.803$	$r = -0.059$ $P = 0.321$	$r = -0.130$ $P = 0.012$	$r = -0.096$ $P = 0.107$	$r = 0.079$ $P = 0.188$	$r = 0.043$ $P = 0.475$	$r = -0.187$ $P = 0.009$	$r = -0.046$ $P = 0.440$
ln LVM, g	$r = 0.154$ $P = 0.009$	$r = -0.491$ $P < 0.001$	$r = 0.154$ $P = 0.009$	$r = 0.189$ $P = 0.001$	$r = 0.016$ $P = 0.786$	$r = 0.209$ $P < 0.001$	$r = 0.209$ $P < 0.001$	$r = 0.233$ $P < 0.001$	$r = 0.328$ $P < 0.001$	$r = 0.301$ $P < 0.001$	$r = 0.155$ $P = 0.009$
ln Concentricity (LVM/EDV)	$r = 0.209$ $P < 0.001$	$r = -0.258$ $P < 0.001$	$r = 0.034$ $P = 0.561$	$r = 0.133$ $P = 0.024$	$r = -0.042$ $P = 0.478$	$r = 0.179$ $P = 0.002$	$r = 0.172$ $P = 0.004$	$r = 0.204$ $P = 0.001$	$r = 0.255$ $P < 0.001$	$r = 0.259$ $P < 0.001$	$r = 0.147$ $P = 0.013$

Weak ($r < 0.3$), moderate ($0.3 \leq r < 0.5$), strong ($r \geq 0.5$) relationship.

BMI, body mass index; EDV, end-diastolic volume; EF, ejection fraction; Hb, hemoglobin; IL-6, interleukin-6; LVM, left ventricular mass index; OH, overhydration; PTH, parathyroid hormone; SBP, systolic blood pressure; sTNF-RI, soluble tumor necrosis factor receptor I; UACR, urinary albumin excretion rate.

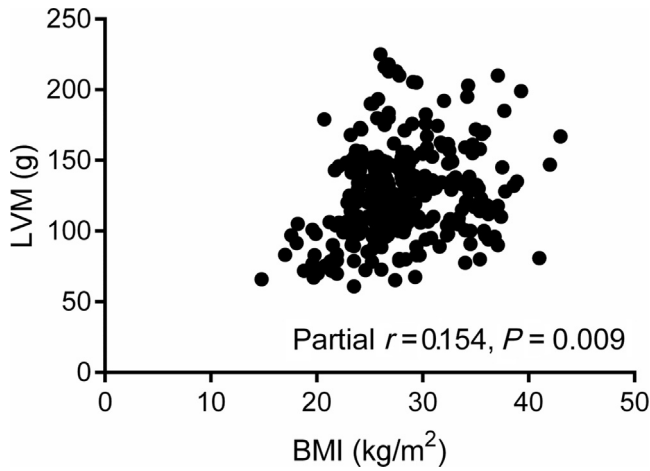


Figure 2. Correlation between body mass index (BMI) and left ventricular mass (LVM).

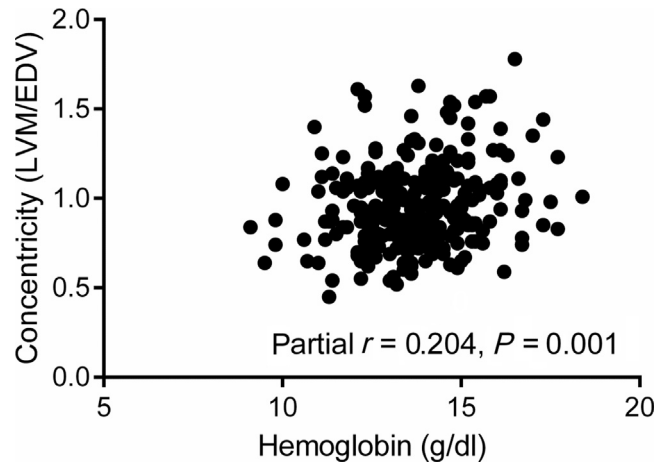


Figure 4. Correlation between hemoglobin and concentricity. LVM/EDV, left ventricular mass index/end-diastolic volume.

DISCUSSION

To our knowledge, this is the first study to examine the LV structure in patients with mild-to-moderate CKD with MRI. Our analyses showed that BMI, SBP, and hemoglobin levels were the key independent determinants of LVM and concentricity.

Previous studies have reported associations of high-sensitivity C-reactive protein, TNF- α , and its receptors with LVH in patients with and without CKD, respectively.^{21,22} Among the markers of inflammation examined in the current study, only sTNF-RI was associated with LVM in the univariate analysis. However, this parameter did not independently contribute to the regression models. With regard to the impact of MBD, studies have suggested a role for increased levels of PTH¹⁰ and low levels of vitamin D.⁹ In recent years, FGF-23, a bone-derived peptide and key regulator of phosphate excretion, was found to induce LV hypertrophy in animal models, and was shown to be related to LVH in CKD patients.¹¹ Some studies have confirmed

this relationship,^{23,24} but others have not.^{25,26} Arguing against a role of FGF-23, no evidence of cardiac alterations was recently reported in patients with FGF-23-related rickets/osteomalacia, who have extremely

Table 6. Linear regression analyses

Ln EDV		
	Stand. β value	P value
$R = 0.432, \text{corr. } R^2 = 0.169, P < 0.001$		
Age	-0.197	0.004
BMI	0.376	<0.001
OH	0.038	0.005
sTNF-RI	-0.038	0.579
Ln LVM		
	Stand. β value	P value
$R = 0.768, \text{corr. } R^2 = 0.565, P < 0.001$		
Age	-0.049	0.349
Sex	-0.558	<0.001
BMI	0.209	<0.001
Smoking	0.086	0.112
Creatinine	0.045	0.617
UACR	0.047	0.403
Hemoglobin	-0.016	0.779
24-h SBP	0.284	<0.001
sTNF-RI	-0.006	0.950
PTH	0.076	0.248
Ln concentricity		
	Stand. β value	P value
$R = 0.510, \text{corr. } R^2 = 0.220, P < 0.001$		
Age	0.159	0.024
Sex	-0.196	0.014
Smoking	0.026	0.100
Creatinine	-0.100	0.402
UACR	0.041	0.583
Hemoglobin	0.012	0.033
24-h SBP	0.189	0.010
sTNF-RI	0.192	0.105
PTH	0.114	0.196

Boldface indicates $P < 0.05$.

BMI, body mass index; corr., corrected; EDV, end-diastolic volume; FGF-23, fibroblast growth factor-23; IL-6, interleukin-6; LVM, left ventricular mass; OH, overhydration; PTH, parathyroid hormone; SBP, systolic blood pressure; Stand., standardized; sTNF-RI, soluble tumor necrosis factor receptor I; UACR, urinary albumin excretion rate.

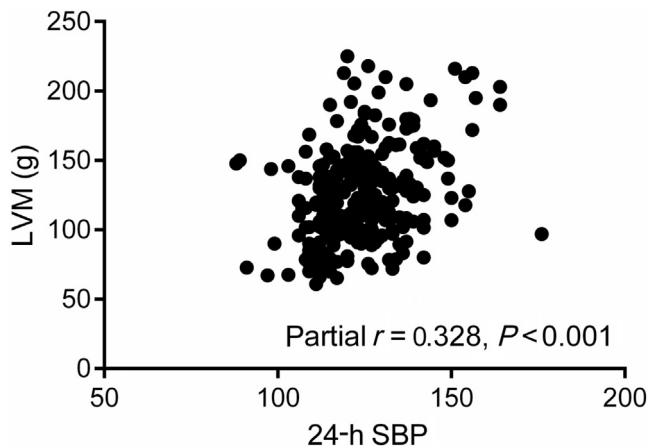


Figure 3. Correlation between 24-hour systolic blood pressure (SBP) and left ventricular mass (LVM).

high circulating FGF-23 levels.²⁶ Similarly, no LVH was recently reported in a novel animal model of hypophosphatemia with high circulating FGF-23 levels.²⁷ We found no relationship between C-terminal or active FGF-23 and LV structure. Interestingly, the authors of a recent meta-analysis came to the conclusion that the previously reported association between FGF-23 and mortality may not be due to direct effects of FGF-23 on the cardiovascular system.²⁸ Furthermore, vitamin D deficiency has been suggested to affect LV structure,⁹ but we could not find evidence for this in our patient sample. The negative outcome of the Paricalcitol Capsules Benefits Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease Stage 3/4 (PRIMO) study, in which active vitamin D therapy failed to cause regression of LVH, also argues against a significant role of vitamin D for CKD-LVH.²⁹ We found PTH related to LV structure only in the univariate analysis, but this parameter also did not contribute to the regression models. We found no association of soluble α -klotho with LV structure. We could also find no evidence for a role of endothelial dysfunction, although, on average, flow-mediated vasodilation was clearly reduced in our patients. Finally, OH was recently described as a determinant of LVH in patients on dialysis.⁷ We found a weak but significant relationship with EDV, but not with LVM or concentricity in our current study.

With regard to BP, it is important to note that almost all of our patients were on antihypertensive therapy. Despite the fact that BP was rather well controlled in our patient sample recruited from secondary (specialist) care, “on-treatment” BP correlated most strongly with LV parameters. There is some evidence, for example, from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, that an SBP goal of <120 mm Hg may achieve better regression of LVH than a BP goal of <140 mm Hg.³⁰ Whether this would also be true for CKD-LVH is unknown and requires a randomized controlled trial. The results from the Systolic Blood Pressure Intervention Trial will further stimulate debate about BP goals in CKD patients.¹⁹ Of note, there is some evidence that mineralocorticoid receptor blockade may have beneficial cardiac effects in patients with CKD.³¹ In our cohort, mineralocorticoid receptor antagonists were rarely used (6%), which presumably reflects the caution that is exercised with these drugs in patients with CKD. Finally, among all the parameters that were determined with the ambulatory device, 24-hour SBP was the variable that was most closely associated with LV structure, and the derived indices central SBP, central augmentation index, and pulse wave velocity did not perform better.

Of note, our patients with mild-to-moderate CKD did not have a high prevalence of anemia. Rather, the

observed relationship between hemoglobin and cardiac structure appeared to be driven by patients with excessively high hemoglobin levels.

The limitations of our study include its cross-sectional nature, which does not allow us to assess time-dependent exposure to the variables investigated. The strengths include the use of MRI as a gold standard technique, the size, which exceeds previous MRI studies in CKD patients, and the large spectrum of parameters included in multivariate analyses.

In conclusion, we found that, in our cohort of patients with mild-to-moderate CKD, almost one-half had evidence of abnormal LV structure. We identified increased BMI, elevated hemoglobin, and elevated 24-hour SBP as key determinants of abnormal LV remodeling. A tailored application of treatment strategies aimed at these risk factors may effectively prevent LV remodeling and, hence, improve outcome.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Correlations of variables not included into regression analysis with LV parameters.

Supplementary material is linked to the online version of the paper at www.kireports.org/.

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