

4-24-2015

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Recommended Citation

Gupta, J., Dominic, E.A., Fink, J.C., Ojo, A.O., Barrows, I.R., et al. (2015) Association between Inflammation and Cardiac Geometry in Chronic Kidney Disease: Findings from the CRIC Study. PLoS ONE 10(4): e0124772.

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RESEARCH ARTICLE

Association between Inflammation and Cardiac Geometry in Chronic Kidney Disease: Findings from the CRIC Study

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OPEN ACCESS

Citation: Gupta J, Dominic EA, Fink JC, Ojo AO, Barrows IR, Reilly MP, et al. (2015) Association between Inflammation and Cardiac Geometry in Chronic Kidney Disease: Findings from the CRIC Study. *PLoS ONE* 10(4): e0124772. doi:10.1371/journal.pone.0124772

Academic Editor: Leighton R James, University of Florida, UNITED STATES

Received: December 18, 2014

Accepted: March 8, 2015

Published: April 24, 2015

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Data Availability Statement: The CRIC GWAS and IBC data are uploaded to dbGAP (Study Accession: phs000524.v1.p1). CRIC data is uploaded to the NIDDK repository according to pre-established requirements and timelines. Phase I baseline data was uploaded to the repository in 2013.

Funding: Dr. Raj is supported by the National Institutes of Health Grants 1R01DK073665-01A1, 1U01DK099924-01 and 1U01DK099914-01. Funding for the CRIC Study was obtained under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases (U01DK060990,

Abstract

Background

Left ventricular hypertrophy (LVH) and myocardial contractile dysfunction are independent predictors of mortality in patients with chronic kidney disease (CKD). The association between inflammatory biomarkers and cardiac geometry has not yet been studied in a large cohort of CKD patients with a wide range of kidney function.

Methods

Plasma levels of interleukin (IL)-1 β , IL-1 receptor antagonist (IL-1RA), IL-6, tumor necrosis factor (TNF)- α , transforming growth factor (TGF)- β , high-sensitivity C-Reactive protein (hs-CRP), fibrinogen and serum albumin were measured in 3,939 Chronic Renal Insufficiency Cohort study participants. Echocardiography was performed according to the recommendations of the American Society of Echocardiography and interpreted at a centralized core laboratory.

U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, and U01DK060902). In addition, this work was supported in part by: the University of Pennsylvania CTSC CTSA UL1 RR-024134, Johns Hopkins University UL1 RR-025005, University of Maryland GCRC M01 RR-16500, Clinical and Translational Science Collaborative of Cleveland, UL1TR000439 from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research, Michigan Institute for Clinical and Health Research (MICHR) UL1RR024986, University of Illinois at Chicago CTSA UL1RR029879, Tulane University Translational Research in Hypertension and Renal Biology P30GM103337, Kaiser Permanente Northern California NIH/NCRR UCSF-CTSI UL1 RR-024131. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Results

LVH, systolic dysfunction and diastolic dysfunction were present in 52.3%, 11.8% and 76.3% of the study subjects, respectively. In logistic regression analysis adjusted for age, sex, race/ethnicity, diabetic status, current smoking status, systolic blood pressure, urinary albumin-creatinine ratio and estimated glomerular filtration rate, hs-CRP (OR 1.26 [95% CI 1.16, 1.37], $p < 0.001$), IL-1RA (1.23 [1.13, 1.34], $p < 0.0001$), IL-6 (1.25 [1.14, 1.36], $p < 0.001$) and TNF- α (1.14 [1.04, 1.25], $p = 0.004$) were associated with LVH. The odds for systolic dysfunction were greater for subjects with elevated levels of hs-CRP (1.32 [1.18, 1.48], $p < 0.001$) and IL-6 (1.34 [1.21, 1.49], $p < 0.001$). Only hs-CRP was associated with diastolic dysfunction (1.14 [1.04, 1.26], $p = 0.005$).

Conclusion

In patients with CKD, elevated plasma levels of hs-CRP and IL-6 are associated with LVH and systolic dysfunction.

Introduction

Left ventricular hypertrophy (LVH) increases the risk of cardiovascular (CV) mortality and morbidity in the general population as well as in patients with chronic kidney disease (CKD). [1,2] Although LVH begins as an adaptive response to pressure or volume overload, it often results in diastolic dysfunction, eventually leading to heart failure. Abnormal cardiac geometry in patients with CKD has been attributed to a number of established risk factors as well as risk factors unique to CKD.[3,4] Evidence from experimental studies indicates that cytokines regulate cardiac remodeling and contractile function.[5,6] However, to date, no large scale study has examined the association between biomarkers of inflammation and cardiac geometry in a multi-racial cohort of subjects with established CKD. Understanding the role of inflammatory molecules in the pathogenesis of heart disease in CKD is important for the design and implementation of targeted anti-inflammatory therapies.

We recently reported that biomarkers of inflammation were inversely associated with measures of kidney function and positively with the magnitude of proteinuria in chronic renal insufficiency cohort (CRIC) study participants.[7] In the same cohort, Park et al [8] found that the risk of LVH was increased among subjects with a cystatin based estimated glomerular filtration rate (eGFR) of less than 30 ml/min per 1.73 m². In the present study, we examined whether systemic inflammation is a predictor of cardiac structure and function independent of the level of kidney function.

Materials and Methods

The CRIC study is an ongoing, multicenter, prospective observational cohort study of men and women with CKD. The design of the CRIC study has been previously reported.[9] All of the 3,939 study participants have provided written informed consent. The study complies with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board at each participating site (University of Pennsylvania, Philadelphia, PA; Johns Hopkins Medicine, Baltimore, MD; University of Maryland, College Park, MD; University Hospitals Case Medical Center, Cleveland, OH; MetroHealth System, Cleveland, OH; Cleveland Clinic Foundation, Cleveland, OH; University of Michigan, Ann Arbor, MI; St. John Hospital and Medical Center,

Grosse Pointe Woods, MI; Wayne State University, Detroit, MI; University of Illinois at Chicago, Chicago, IL; Tulane University, New Orleans, LA; Kaiser Foundation Research Institute, Oakland, CA).

CRIC data collection

Demographic characteristics, medical history, smoking status, weight, height, body mass index (BMI) and use of medications including statins, angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were recorded at baseline. Serum creatinine was measured by the Jaffe method on a Beckman Synchron System. eGFR was computed using the Modification of Diet in Renal Disease estimating equation.[10] Proteinuria was measured as the ratio of albumin to creatinine in the urine (UACR).

Measurement of biomarkers of inflammation

Biomarker measurements were performed as described earlier.[7] Briefly, high sensitivity sandwich ELISAs (Quantikine HS, R&D Systems, Minneapolis, MN) were used to measure plasma interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α levels. Standard sandwich ELISAs (Quantikine, R&D Systems) were used to quantify IL-1 receptor antagonist (IL-1RA) and transforming growth factor (TGF)- β levels. Integrated performance of IL-1 β , IL-1RA, IL-6, and TNF- α ELISAs were implemented using a robotic liquid handling platform (Biomek FXp, Beckman Coulter, Brea, CA). All cytokine assays were performed in duplicates and mean values used in the analysis. High sensitivity C-reactive protein (hs-CRP) and fibrinogen were quantified in EDTA plasma samples using specific laser-based immunonephelometric methods on the BNII (Siemens Healthcare Diagnostics, Deerfield, IL).

Echocardiography

Echocardiography was performed on all study participants within 14 months of enrollment in the study. Studies were performed according to the recommendations of the American Society of Echocardiography and interpreted at a centralized, quality-controlled quantitative echocardiography core laboratory.[11] LV mass was calculated using the area-length method and indexed to height^{2.7} (LVMI).[11,12] LVH was defined as LV mass/height^{2.7} \geq 47 g/m^{2.7} in women and \geq 50 g/m^{2.7} in men.[13] Relative wall thickness (RWT) was calculated as $2 \times$ posterior wall thickness/LV internal linear dimension in diastole. Based on the LVMI and RWT measurements,[11] four geometric patterns were described:

- a. normal (normal LVMI and normal RWT)
- b. concentric remodeling (normal LVMI and increased RWT)
- c. eccentric hypertrophy (abnormally increased LVMI and normal RWT), and
- d. concentric hypertrophy (abnormally increased LVMI and increased RWT).

Mitral inflow E- and A-wave velocities, E-wave deceleration time, and pulmonary venous reverse A-wave duration were used to categorize LV diastolic function, using well-established criteria.[14] LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were calculated using the modified biplane method. Ejection fraction was calculated as (LVEDV-LVESV)/LVEDV. Systolic dysfunction was defined as ejection fraction <45%.[8,15]

Statistical Analyses

Descriptive statistics for selected demographic and clinical characteristics of the study population stratified by the presence of LVH are presented. Values are presented as frequency (percentage), mean (standard deviation; SD) and median (inter-quartile range; IQR) as appropriate. Two sample t-test, Wilcoxon rank-sum test and Pearson's chi-squared test were used to compare continuous and categorical variables across the LVH strata. The association of inflammatory biomarkers with the presence of LVH, systolic dysfunction and diastolic dysfunction were examined with logistic regression models. Multinomial logistic regression was used to examine the association between inflammatory biomarkers and cardiac geometry (the outcomes of concentric hypertrophy, concentric remodeling, and eccentric hypertrophy, with normal cardiac geometry as reference). Linear regression models were used to investigate the association of the inflammatory biomarkers with LVMI and ejection fraction. All models were adjusted for age, sex, race/ethnicity, diabetic status, current smoking status, systolic blood pressure, eGFR and log transformed UACR. The addition of ACEI-ARB use as a covariate did not influence the effect estimates and p-values and therefore it was not included in the final models. All principal predictors (hs-CRP, fibrinogen, serum albumin, IL-1 β , IL-1RA, IL-6, TNF- α and TGF- β) were log-transformed and expressed in standard deviation units for use in regression analyses. Bonferroni's correction was used to adjust for multiple comparisons. All analyses were performed using the SAS statistical software (version 9.3; SAS Inc., Cary, NC).

Results

Demographic and clinical characteristics of the participants categorized by the presence of LVH are shown in [Table 1](#). LVH was present in 1,631 (52.3%) participants and 16.8% of those with LVH had ejection fraction <45%. Those with LVH were more likely to be female, non-Hispanic Black, older in age, former smoker, diabetic, hypertensive and with reduced kidney function when compared to those without LVH. As a group, they also had a higher systolic BP and a larger BMI, and were more likely to report ACEI-ARB use than the group without LVH. Subjects with LVH also had lower levels of serum albumin and higher levels of inflammatory biomarkers (except TGF- β) on an average compared to those without LVH.

In multivariable linear regression analyses, hs-CRP [regression coefficient = 1.50 (95% Confidence intervals: 1.05, 1.96), $p < 0.001$], IL-1 β [0.76 (0.30, 1.23), $p = 0.0010$], IL-1RA [1.30 (0.84, 1.75), $p < 0.0001$], IL-6 [1.53 (1.05, 2.01), $p < 0.001$] and TNF- α [0.72 (0.23, 1.21), $p = 0.004$] were associated with LVMI ([Table 2](#)). Serum albumin level was negatively associated with LVMI [-1.24 (-1.76, -0.71), $p < 0.001$]. hs-CRP [-0.75 (-1.05, -0.46), $p < 0.001$] and IL-6 [-0.91 (-1.22, -0.60), $p < 0.001$] were both negatively associated with ejection fraction.

LVH, systolic dysfunction and diastolic dysfunction were present in 1,631 (52.3%), 411 (11.8%) and 2,330 (76.3%) of the participants, respectively. ([Table 3](#)) Adjusted logistic regression analysis showed that hs-CRP [Odds Ratio = 1.26 (95% Confidence intervals: 1.16, 1.37), $p < 0.001$], IL-1RA [1.23 (1.13, 1.34), $p < 0.001$], IL-6 [1.25 (1.14, 1.36), $p < 0.001$], and TNF- α [1.14 (1.04, 1.25), $p = 0.004$] were associated with the presence of LVH. The odds for having systolic dysfunction were greater for higher levels of hs-CRP [1.32 (1.18, 1.48), $p < 0.001$] and IL-6 [1.34 (1.21, 1.49), $p < 0.001$]. Only hs-CRP [1.14 (1.04, 1.26), $p = 0.005$] was associated with the presence of diastolic dysfunction.

Concentric remodeling, concentric hypertrophy and eccentric hypertrophy were present in 855 (28.6%), 1,102 (36.9%) and 447 (15.0%) participants, respectively. ([Table 4](#)) When inflammatory markers were examined for their associations with cardiac geometry using an adjusted multinomial logistic regression model, hs-CRP [Odds Ratio = 1.32 (95% Confidence Intervals: 1.17, 1.49), $p < 0.001$], IL-1 β [1.24 (1.1, 1.4), $p < 0.001$], IL-1RA [1.4 (1.24, 1.58), $p < 0.001$] and

Table 1. Baseline demographic and clinical characteristics of the study cohort categorized by the presence of LVH.

Variables presented as n (%), mean ± standard deviation and median (interquartile range) as appropriate	LVH absent n = 1488	LVH present n = 1631	p-value
Females	647 (43.5)	785 (48.1)	0.009
Race/ethnicity			<0.001
Non-Hispanic white	796 (53.5)	499 (30.6)	
Non-Hispanic Black	512 (34.4)	790 (48.4)	
Hispanic	117 (7.9)	281 (17.2)	
Other	63 (4.2)	61 (3.7)	
Diabetes	524 (35.2)	956 (58.6)	<0.001
Hypertension	1153 (77.5)	1522 (93.3)	<0.001
Ever smoked	753 (50.6)	907 (55.6)	0.005
Smoke now	174 (11.7)	206 (12.6)	0.42
ACEI-ARB use	957 (64.6)	1169 (72.2)	<0.001
Age (years)	55.7 ± 11.6	59 ± 10.2	<0.001
Systolic BP (mmHg)	121.7 ± 18.8	134 ± 22.5	<0.001
Diastolic BP (mmHg)	71.2 ± 11.8	72.1 ± 13.5	0.07
BMI (kg/m ²)	28.8 ± 5.8	34 ± 7.5	<0.001
eGFR (ml/min/1.73m ²)	46.1±13.5	40.2 (13)	<0.001
UACR (mcg/mg)	21.1 (5.9, 203.8)	109.2 (14.7, 868.2)	<0.001
Total cholesterol (mmol/L)	4.8 ± 1.11	4.7± 1.2	0.09
Hemoglobin (g/L)	130 ± 17.0	122 ±18.0	<0.001
hs-CRP (nmol/L)	18.1 (8.6, 44.8)	27.6 (11.4, 66.7)	<0.001
Fibrinogen (µmol/L)	11.2 (9.4, 12.9)	12.6 (10.6, 14.7)	<0.001
Albumin (g/L)	41.0 (38.1, 43.0)	39.0 (36.0, 42.0)	<0.001
IL-1β (pg/ml)	0 (0, 0.9)	0.3 (0, 1.5)	<0.001
IL-1RA (pg/ml)	599.7 (328.0, 1298.5)	809.2 (424.7, 1646.7)	<0.001
IL-6 (pg/ml)	1.4 (0.9, 2.4)	2.1 (1.4, 3.3)	<0.001
TNF-α (pg/ml)	1.9 (1.3, 2.8)	2.4 (1.7, 3.4)	<0.001
TGF-β (pg/ml)	10.7 (6.2, 18.1)	10.8 (6.5, 17.6)	0.7

LVH was defined as LV mass/height^{2.7} ≥ 47 g/m^{2.7} in women and ≥50 g/m^{2.7} in men. UACR = Urine albumin to creatinine ratio

doi:10.1371/journal.pone.0124772.t001

IL-6 [1.29 (1.13, 1.47), p<0.001] were each associated with concentric hypertrophy. Only TGF-β was associated with a higher risk of concentric remodeling [1.21 (1.09, 1.35), p<0.001]. Eccentric hypertrophy was positively associated with hs-CRP ([1.38 (1.20, 1.58), p<0.001], IL-1RA [1.24 (1.08, 1.43), p = 0.002] and IL-6 [1.31 (1.13, 1.52), p<0.001], but negatively associated with serum albumin level [0.78 (0.67, 0.91), p = 0.002].

Discussion

A number of investigators have reported an association between inflammation and increased CV mortality in CKD.[16,17] In this study, we examined the association of circulating biomarkers of inflammation with echocardiographically determined cardiac structure and function using CRIC study participants and found significant associations between several inflammatory biomarkers and LVH and systolic dysfunction after adjusting for several traditional CV risk factors as well as measures of kidney function. Of all biomarkers, hs-CRP and IL-6 were more consistently associated with abnormal cardiac geometry and contractile dysfunction. Lower serum albumin was associated with LVMI and eccentric hypertrophy. Thus,

Table 2. Adjusted linear regression models showing the association of inflammatory biomarkers with LVMI and ejection fraction.

Predictor	Outcome			
	LVMI; n = 3,119		Ejection Fraction %; n = 3,484	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
hs-CRP	1.5 (1.05, 1.96)	<0.001*	-0.75 (-1.05, -0.46)	<0.001*
Fibrinogen	0.2 (-0.27, 0.67)	0.41	-0.2 (-0.51, 0.10)	0.19
Albumin	-1.24 (-1.76,-0.71)	<0.001*	0.03 (-0.31, 0.37)	0.84
IL-1β	0.76 (0.30, 1.23)	0.001*	-0.25 (-0.55, 0.05)	0.11
IL-1RA	1.3 (0.84, 1.75)	<0.001*	-0.18 (-0.47, 0.12)	0.24
IL-6	1.53 (1.05, 2.01)	<0.001*	-0.91 (-1.22, -0.60)	<0.001*
TNF-α	0.72 (0.23, 1.21)	0.004*	-0.12 (-0.44, 0.19)	0.44
TGF-β	-0.38 (-0.83, 0.07)	0.1	0.04 (-0.25, 0.33)	0.77

Left ventricular mass index (LVMI) was calculated using the area-length method and indexed to height^{2.7}

* Significant after Bonferroni correction for multiple comparisons (corrected p-value: 0.05/8 = 0.006).

doi:10.1371/journal.pone.0124772.t002

this study shows that inflammation is a potential modulator of cardiac remodeling and function in patients with CKD.

Laboratory-based studies have shown that cytokines promote cardiac remodeling by stimulating sarcomeric protein synthesis, enhancing fetal gene expression, altering extracellular matrix degradation and triggering apoptosis.[6,18,19] Although most of the circulating cytokines are secreted from activated macrophages and lymphocytes, adipocytes and skeletal muscle are also possible sources of these biomolecules.[20,21] Proinflammatory cytokines are not constitutively expressed in the myocardium, but are upregulated in response to myocardial injury and may contribute to circulating levels.[22] CRP is a predictor of CVD in the general population and in patients with CKD.[23,24] In a cohort of resistant hypertensive patients, microalbuminuria and high CRP were independently associated with the occurrence of LVH.[25] In a

Table 3. Adjusted logistic regression models showing the association of inflammatory biomarkers with LVH, systolic dysfunction and diastolic dysfunction.

Predictor	Outcome					
	Left ventricular hypertrophy; n = 3,119		Systolic dysfunction; n = 3,484		Diastolic dysfunction; n = 3,053	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
hs-CRP	1.26 (1.16, 1.37)	<0.001*	1.32 (1.18, 1.48)	<0.001*	1.14 (1.04, 1.26)	0.005*
Fibrinogen	1.07 (0.98, 1.17)	0.14	1.02 (0.91, 1.15)	0.76	1.12 (1.02, 1.23)	0.01
Albumin	0.88 (0.80, 0.97)	0.009	0.97 (0.86, 1.09)	0.57	1 (0.9, 1.11)	0.94
IL-1β	1.11 (1.03, 1.21)	0.01	1.04 (0.93, 1.17)	0.47	1.04 (0.95, 1.15)	0.39
IL-1RA	1.23 (1.13, 1.34)	<0.001*	1.04 (0.94, 1.16)	0.45	1.1 (1, 1.21)	0.05
IL-6	1.25 (1.14, 1.36)	<0.001*	1.34 (1.21, 1.49)	<0.001*	1.06 (0.95, 1.17)	0.3
TNF-α	1.14 (1.04, 1.25)	0.004*	1.09 (0.97, 1.23)	0.14	1.12 (1.01, 1.24)	0.03
TGF-β	0.92 (0.85, 1.00)	0.05	1.07 (0.96, 1.19)	0.24	1.01 (0.92, 1.11)	0.78

LVH was defined as LV mass/height^{2.7} ≥ 47 g/m^{2.7} in women and ≥50 g/m^{2.7} in men

Systolic dysfunction was defined as ejection fraction <45%

* Significant after Bonferroni correction for multiple comparisons (corrected p-value: 0.05/8 = 0.006).

doi:10.1371/journal.pone.0124772.t003

Table 4. Adjusted multinomial logistic regression models showing the association of inflammatory biomarkers with cardiac geometry.

Predictor	Outcome					
	Concentric hypertrophy; n = 1,102		Concentric remodeling; n = 855		Eccentric hypertrophy; n = 447	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
hs-CRP	1.32 (1.17, 1.49)	<0.001*	1.10 (0.98, 1.24)	0.1	1.38 (1.20, 1.58)	<0.001*
Fibrinogen	1.02 (0.91, 1.15)	0.76	1.00 (0.90, 1.12)	0.95	1.2 (1.01, 1.43)	0.03
Albumin	0.93 (0.81, 1.07)	0.29	0.99 (0.86, 1.13)	0.85	0.78 (0.67, 0.91)	0.002*
IL-1 β	1.24 (1.1, 1.4)	<0.001*	1.08 (0.97, 1.22)	0.17	1.09 (0.95, 1.25)	0.23
IL-1RA	1.40 (1.24, 1.58)	<0.001*	1.15 (1.02, 1.29)	0.02	1.24 (1.08, 1.43)	0.002*
IL-6	1.29 (1.13, 1.47)	<0.001*	1.08 (0.95, 1.23)	0.27	1.31 (1.13, 1.52)	<0.001*
TNF- α	1.14 (1.01, 1.3)	0.04	0.96 (0.85, 1.09)	0.53	1.07 (0.92, 1.24)	0.4
TGF- β	1.05 (0.93, 1.17)	0.45	1.21 (1.09, 1.35)	<0.001*	1.01 (0.88, 1.15)	0.93

* Significant after Bonferroni correction for multiple comparisons (corrected p-value: 0.05/8 = 0.006).

doi:10.1371/journal.pone.0124772.t004

small study, involving 104 maintenance hemodialysis patients, hs-CRP and systolic BP were independent predictors of LVH. [26] Whether CRP is just a marker of overall inflammatory state or a direct mediator of LVH is currently uncertain.

Based on LVMI and RWT, four patterns of cardiac geometry were recognized. Abnormal cardiac geometry is associated with CV events in patients with CKD.[27,28] In the current study, the presence of both concentric and eccentric hypertrophy was associated with elevated levels of hs-CRP and inflammatory cytokines. Circulating IL-6 was associated with the presence of both concentric and eccentric hypertrophy. In two hypertensive rat models, Kurdi et al. showed that IL-6 and leukemia inhibitory factor contributed to angiotensin II-dependent LVH. [29] *In vitro* studies show that IL-6 mediates cardiac myocyte hypertrophy by an auto-crine pathway and fibroblast proliferation by a paracrine pathway.[5,30] In the current study, low serum albumin was associated with LVMI as well as with the presence of eccentric hypertrophy. A strong association between serum albumin and LV dilation has been reported in end-stage renal disease patients.[31] The link between serum albumin and cardiac geometry could be a reflection of underlying inflammation as well as other associated comorbidities such as protein energy wasting.

Heart failure may be due to systolic or diastolic dysfunction, or both.[32] In the present study, ejection fraction was negatively associated with hs-CRP and IL-6. The contractile function of isolated cardiac myocytes is modulated by cytokines through activation of the neutral sphingomyelinase pathway and by NO-mediated blunting of β -adrenergic signaling.[33,34] Pro-inflammatory cytokines may also promote diastolic heart failure through down-regulation of diastolic calcium reuptake by sarcoplasmic reticulum.[35] However, in our study only hs-CRP was associated with an increased risk for diastolic dysfunction.

The cross-sectional associations reported in this study should be interpreted with caution. Cytokines are pleiotropic in their actions, and exhibit interactive cascades in which they induce or repress their own synthesis as well as that of other cytokines and cytokine receptors.[36] An important component of the inflammatory cascade is the acute-phase response, which is regulated by cytokines such as IL-6. Zoccali et al.[37] showed that an inflammation score based on CRP, IL-6, IL-1 β , IL-18 and TNF- α was not superior to IL-6 in predicting mortality in patients with ESRD. In the present study as well, IL-6 emerged as a strong and independent predictor of unfavorable cardiac geometry.

A number of studies have demonstrated that single measures of various inflammatory biomarkers at baseline are important determinants of subsequent adverse outcomes in subjects with kidney disease.[37,38] In a study involving 62 subjects without kidney disease, single measures of hs-CRP, TNF- α , IL-8, and soluble TNF receptor I and II accurately reflected the inflammatory status over a 4–6-month period.[39] However, intra-individual variation in inflammatory biomarkers is also reported in subjects with and without kidney disease.[40–42] In the Mapping of Inflammatory Markers in Chronic Kidney Disease (MIMICK) Study, inflammatory markers were measured over 3 months in 228 hemodialysis patients. Baseline CRP level was highly correlated with time-averaged CRP as well as with the median of serial CRP values.[43] However, in the multivariate Cox model, median CRP level was associated more strongly with mortality than a single baseline value, indicating that serial CRP values over time is superior in estimation of the patient's risk profile.[43]

Our study has a number of strengths which include: (a) a large cohort of patients from different races/ethnicities with a broad range of kidney function; (b) examination of a large panel of biomarkers with pro- and anti-inflammatory properties; and (c) consideration of traditional CV risk factors. Echocardiography performed using a standardized protocol, which included quality control of the measurements, is an added strength. However, these findings should be considered within the context of some limitations: (a) this is a cross-sectional analysis and hence temporal associations and causality cannot be inferred; (b) biomarkers were measured at one time point only; and (c) some echocardiographic parameters were not available in a subset of study participants due to technical difficulties.

Conclusions

To summarize, using a large cohort of well characterized CKD subjects, this study demonstrates that abnormal cardiac structure and function are associated with specific biomarkers of inflammation. Specifically, elevated hs-CRP and IL-6 were independently and consistently associated with LVH and systolic dysfunction. Low serum albumin was associated with higher LVMI and eccentric hypertrophy. Among the pro-inflammatory biomarkers studied, IL-6 appears to best capture the inflammatory status as well as the association with adverse cardiac remodeling in CKD patients. The prognostic implications and the utility of IL-6 as a therapeutic target warrant further investigation.

Acknowledgments

CRIC Study Investigators not specifically listed as authors: Lawrence J. Appel, MD, MPH; Alan S. Go, MD; Jiang He, MD, PhD; James P. Lash, MD; Mahboob Rahman, MD.

Author Contributions

Conceived and designed the experiments: DSR. Analyzed the data: JG. Wrote the paper: JG EAD DSR. Critically evaluated the manuscript and provided scientific input: JCF AOO IRB MPR RRT MMJ SER MW SSP MGK HIF JWK.

References

1. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giaccone G, Stancanelli B et al. (2004) Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int* 65: 1492–1498. PMID: [15086493](#)
2. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH (1991) Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114: 345–352. PMID: [1825164](#)

3. Middleton RJ, Parfrey PS, Foley RN (2001) Left ventricular hypertrophy in the renal patient. *J Am Soc Nephrol* 12: 1079–1084. PMID: [11316868](#)
4. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T et al. (2011) FGF23 induces left ventricular hypertrophy. *J Clin Invest* 121: 4393–4408. doi: [10.1172/JCI46122](#) PMID: [21985788](#)
5. Fredj S, Bescond J, Louault C, Delwail A, Lecron JC, Potreau D (2005) Role of interleukin-6 in cardiomyocyte/cardiac fibroblast interactions during myocyte hypertrophy and fibroblast proliferation. *J Cell Physiol* 204: 428–436. PMID: [15717324](#)
6. Yokoyama T, Nakano M, Bednarczyk JL, McIntyre BW, Entman M, Mann DL (1997) Tumor necrosis factor-alpha provokes a hypertrophic growth response in adult cardiac myocytes. *Circulation* 95: 1247–1252. PMID: [9054856](#)
7. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M et al. (2012) Association between Albuminuria, Kidney Function, and Inflammatory Biomarker Profile. *Clin J Am Soc Nephrol* 7: 1938–1946. doi: [10.2215/CJN.03500412](#) PMID: [23024164](#)
8. Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE et al. (2012) Associations between Kidney Function and Subclinical Cardiac Abnormalities in CKD. *J Am Soc Nephrol* 23: 1725–1734. PMID: [22935481](#)
9. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J et al. (2003) The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. *J Am Soc Nephrol* 14: S148–S153. PMID: [12819321](#)
10. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S et al. (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 145: 247–254. PMID: [16908915](#)
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440–1463. PMID: [16376782](#)
12. Fox ER, Taylor HA Jr, Benjamin EJ, Ding J, Liebson PR, Arnett D et al. (2005) Left ventricular mass indexed to height and prevalent MRI cerebrovascular disease in an African American cohort: the Atherosclerotic Risk in Communities study. *Stroke* 36: 546–550. PMID: [15662040](#)
13. de SG, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH (1995) Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol* 25: 1056–1062. PMID: [7897116](#)
14. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA et al. (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 22: 107–133. doi: [10.1016/j.echo.2008.11.023](#) PMID: [19187853](#)
15. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR et al. (2008) Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 359: 2456–2467. doi: [10.1056/NEJMoa0805450](#) PMID: [19001508](#)
16. Rao M, Guo D, Perianayagam MC, Tighiouart H, Jaber BL, Pereira BJ et al. (2005) Plasma interleukin-6 predicts cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 45: 324–333. PMID: [15685511](#)
17. Rogacev KS, Seiler S, Zawada AM, Reichart B, Herath E, Roth D et al. (2011) CD14++CD16+ monocytes and cardiovascular outcome in patients with chronic kidney disease. *Eur Heart J* 32: 84–92. doi: [10.1093/eurheartj/ehq371](#) PMID: [20943670](#)
18. Krown KA, Page MT, Nguyen C, Zechner D, Gutierrez V, Comstock KL et al. (1996) Tumor necrosis factor alpha-induced apoptosis in cardiac myocytes. Involvement of the sphingolipid signaling cascade in cardiac cell death. *J Clin Invest* 98: 2854–2865. PMID: [8981934](#)
19. Wollert KC, Drexler H (2001) The role of interleukin-6 in the failing heart. *Heart Fail Rev* 6: 95–103. PMID: [11309528](#)
20. Wing MR, Yang W, Teal V, Navaneethan S, Tao K, Ojo A et al. (2014) Race modifies the association between adiposity and inflammation in patients with chronic kidney disease: Findings from the chronic renal insufficiency cohort study. *Obesity (Silver Spring)* 22: 1359–1366. doi: [10.1002/oby.20692](#) PMID: [24415732](#)
21. Raj DSC, Dominic EA, Pai A, Osman F, Morgan M, Pickett G et al. (2005) Skeletal muscle, cytokines and oxidative stress in End-stage renal disease. *Kidney Int* 68: 2338–2344. PMID: [16221238](#)
22. Mann DL (2003) Stress-activated cytokines and the heart: from adaptation to maladaptation. *Annu Rev Physiol* 65: 81–101. doi: [10.1146/annurev.physiol.65.092101.142249](#);092101.142249 [pii]. PMID: [12500970](#)

23. Folsom AR, Aleksic N, Catellier D, Juneja HS, Wu KK (2002) C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J* 144: 233–238. PMID: [12177639](#)
24. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ et al. (2005) C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 68: 766–772. PMID: [16014054](#)
25. Salles GF, Fiszman R, Cardoso CR, Muxfeldt ES (2007) Relation of left ventricular hypertrophy with systemic inflammation and endothelial damage in resistant hypertension. *Hypertension* 50: 723–728. PMID: [17635853](#)
26. Monfared A, Salari A, Kazemnezhad E, Lebadhi M, Khosravi M, Mehrjardi NK et al. (2013) Association of left ventricular hypertrophy with high-sensitive C-reactive protein in hemodialysis patients. *Int Urol Nephrol* 45: 1679–1686. doi: [10.1007/s11255-012-0375-x](#) PMID: [23306861](#)
27. Eckardt KU, Scherhag A, Macdougall IC, Tsakiris D, Clyne N, Locatelli F et al. (2009) Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. *J Am Soc Nephrol* 20: 2651–2660. doi: [10.1681/ASN.2009060631](#) PMID: [19850955](#)
28. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE (1995) The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *Journal of the American Society of Nephrology* 5: 2024–2031. PMID: [7579050](#)
29. Kurdi M, Randon J, Cerutti C, Bricca G (2005) Increased expression of IL-6 and LIF in the hypertrophied left ventricle of TGR(mRen2)27 and SHR rats. *Mol Cell Biochem* 269: 95–101. PMID: [15786720](#)
30. Sano M, Fukuda K, Kodama H, Pan J, Saito M, Matsuzaki J et al. (2000) Interleukin-6 family of cytokines mediate angiotensin II-induced cardiac hypertrophy in rodent cardiomyocytes. *J Biol Chem* 275: 29717–29723. PMID: [10843995](#)
31. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE (1996) Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *Journal of the American Society of Nephrology* 7: 728–736. PMID: [8738808](#)
32. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT et al. (2006) Systolic and diastolic heart failure in the community. *JAMA* 296: 2209–2216. PMID: [17090767](#)
33. Oral H, Dorn GW, Mann DL (1997) Sphingosine mediates the immediate negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian cardiac myocyte. *J Biol Chem* 272: 4836–4842. PMID: [9030540](#)
34. Gulick T, Chung MK, Pieper SJ, Lange LG, Schreiner GF (1989) Interleukin 1 and tumor necrosis factor inhibit cardiac myocyte beta-adrenergic responsiveness. *Proc Natl Acad Sci U S A* 86: 6753–6757. PMID: [2549546](#)
35. Wu CK, Lee JK, Chiang FT, Yang CH, Huang SW, Hwang JJ et al. (2011) Plasma levels of tumor necrosis factor-alpha and interleukin-6 are associated with diastolic heart failure through downregulation of sarcoplasmic reticulum Ca²⁺ ATPase. *Crit Care Med* 39: 984–992. doi: [10.1097/CCM.0b013e31820a91b9](#) PMID: [21263314](#)
36. Feghali CA, Wright TM (1997) Cytokines in acute and chronic inflammation. *Front Biosci* 2: d12–d26. PMID: [9159205](#)
37. Zoccali C, Tripepi G, Mallamaci F (2006) Dissecting inflammation in ESRD: do cytokines and C-reactive protein have a complementary prognostic value for mortality in dialysis patients? *J Am Soc Nephrol* 17: S169–S173. 17/12_suppl_3/S169 [pii];doi: [10.1681/ASN.2006080910](#) PMID: [17130257](#)
38. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ et al. (2005) C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 68: 766–772. PMID: [16014054](#)
39. Navarro SL, Brasky TM, Schwarz Y, Song X, Wang CY, Kristal AR et al. (2012) Reliability of serum biomarkers of inflammation from repeated measures in healthy individuals. *Cancer Epidemiol Biomarkers Prev* 21: 1167–1170. 1055–9965. doi: [10.1158/1055-9965.EPI-12-0110](#) PMID: [22564866](#)
40. DeGoma EM, French B, Dunbar RL, Allison MA, Mohler ER III, Budoff MJ (2012) Intraindividual variability of C-reactive protein: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis* 224: 274–279. doi: [10.1016/j.atherosclerosis.2012.07.017](#) PMID: [22846611](#)
41. den Elzen WP, van Manen JG, Boeschoten EW, Krediet RT, Dekker FW (2006) The effect of single and repeatedly high concentrations of C-reactive protein on cardiovascular and non-cardiovascular mortality in patients starting with dialysis. *Nephrol Dial Transplant* 21: 1588–1595. PMID: [16449284](#)
42. Meuwese CL, Snaedal S, Halbesma N, Stenvinkel P, Dekker FW, Qureshi AR et al. (2011) Trimestral variations of C-reactive protein, interleukin-6 and tumour necrosis factor-alpha are similarly associated with survival in haemodialysis patients. *Nephrol Dial Transplant* 26: 1313–1318. doi: [10.1093/ndt/gfq557](#) PMID: [20846939](#)

43. Snaedal S, Heimburger O, Qureshi AR, Danielsson A, Wikstrom B, Fellstrom B et al. (2009) Comorbidity and acute clinical events as determinants of CRP variation in hemodialysis patients: implications on patient survival. *Am J Kidney Dis* 53:–1033.