https://nephropathol.com DOI: 10.34172/jnp.2022.18393 J Nephropathol. 2023;12(2):e18393

Journal of Nephropathology

Determinants of left ventricular diastolic dysfunction in hemodialysis patients

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 4 July 2022
Accepted: 23 August 2022
Published online: 3 September 2022

Keywords:
Aortic stenosis
Atherosclerosis
C-reactive protein
Calcification
Total antioxidant capacity
Left ventricular diastolic dysfunction

ABSTRACT

Introduction: Chronic kidney disease (CKD) induces changes in the myocardium known to influence morbidity and mortality, most severe in patients with end stage renal disease.
Objectives: The working hypothesis was that in patients on chronic hemodialysis the prevalence of left ventricular diastolic dysfunction is correlated with the inflammatory, oxidative, metabolic, nutritional, and atherosclerotic status.
Patients and Methods: An observational study was performed on 51 patients (age 59.76 ± 13.24 years) on hemodialysis treatment. Transthoracic cardiac ultrasound was conducted to evaluate LVDD. The burden of cardiac and arterial atherosclerosis was evaluated by cardiac ultrasound (aortic and mitral valve calcifications), vascular ultrasound (carotid and femoral atheroma plaques, common carotid intima-media thickness), and by abdominal radiography (aortic calcification score). Demographic and anthropometric parameters were determined. Blood samples were used to determine laboratory parameters reflecting the inflammatory, oxidative, and metabolic/nutrition status.
Results: LVDD is positively correlated with the serum level of C-reactive protein (CRP) ($P=0.04$), the total antioxidant capacity of the serum ($P=0.04$), the presence ($P=0.022$) and number ($P=0.04$) of femoral plaques, the aortic calcification score ($P=0.02$), aortic valve stenosis ($P=0.037$), aortic annulus calcifications ($P=0.02$) and mitral valve calcifications ($P=0.041$). After the removal of the main confounder, degenerative aortic stenosis, only the associations with serum total antioxidant capacity ($P=0.04$) and aortic calcification score ($P=0.02$) maintain their statistical significance.
Conclusion: LVDD is positively correlated with inflammation and oxidative stress markers and with the severity of aortic calcification.

Original Article

Implication for health policy/practice/research/medical education:
In patients on chronic hemodialysis, the prevalence of LVDD is positively correlated with inflammation and oxidative stress markers and with the severity of aortic calcification. The purpose of designing therapeutic strategies is to prevent or slow the course of LVDD, thereby influencing the cardiovascular and general outcomes of these patients.

Please cite this paper as: Dragoş D, Timofte D, Ionescu D, Balcangiu-Stroescu AE, Ghenu MI, Vacaroiu IA, Manea MM. Determinants of left ventricular diastolic dysfunction in hemodialysis patients. J Nephropathol. 2023;12(2):e18393. DOI: 10.34172/jnp.2022.18393.

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Introduction

Left ventricular diastolic dysfunction (LVDD) is frequent in Chronic kidney disease (CKD) patients (1), particularly in those on hemodialysis (2). Multiple cardiac/myocardial anomalies acknowledged to exist in CKD patients may explain it (3), including (a) left ventricular hypertrophy (LVH) (4), which is an early occurrence during the course of CKD (5), has a high prevalence in CKD patients and increases death risk (1); (b) myocardial fibrosis as a consequence of both traditional and CKD-associated risk factors (6); (c) wall thickening of the intramyocardial arterioles (7).

Multiple factors seem to concur in inducing these structural changes, including (a) Those increasing the preload (associated with eccentric LVH and increased length of cardiomyocytes), such as hypervolemia, anemia, and the augmented cardiac output demanded by the arteriovenous fistulas or grafts that provide vascular access for hemodialysis (8); (b) Those raising afterload (associated with concentric LVH and increased thickness of cardiomyocytes) – by augmenting arterial impedance due to high blood pressure and calcification-related arterial wall stiffening (5); (c) Others, including inflammation (5,9–11), oxidative stress (5), anemia (12), and metabolic factors, the latter being primarily related to disordered bone and mineral metabolism: increased serum levels of calcium (13), phosphates (13,14), calcium × phosphate product (13), and parathormone (8,13,15), and vitamin D deficiency (16).

Objectives

This study aimed at uncovering the clinically relevant correlates (which might include putative determinants) of LVDD in hemodialysis patients, with the perspective that they might constitute in the future the basis for prevention programs or interventions.

Patients and Methods

The present study is an observational study performed on 51 patients (30 males, 21 females, age 59.76 ± 13.24 years) on hemodialysis treatment (for 2-84 months, with an average ± standard deviation of 40.76 ± 21.64 months, with an ultrafiltration of 1.95 ± 0.93 L) in the hemodialysis department of the university emergency hospital, Bucharest, Romania.

The diagnosis of LVDD was made according to the current European and American guidelines (17) as they are readily applicable in clinical practice, well correlated with invasive measurements, and reliable in predicted outcome (18).

The imaging atherosclerosis markers (IAMs) employed in our study were; 1. valvular calcifications (both aortic and mitral), estimated by transthoracic cardiac ultrasound, and 2. arterial atherosclerosis burden reflected by: (a) atheroma plaques (both carotid and femoral) and common carotid intima-media thickness, evaluated by vascular ultrasound, and (b) aortic calcification score as defined by Kauppila et al (19), calculated on lateral lumbar films (in which the spine was visible from eleventh thoracic to the second sacral vertebra).

Certified, experienced sonographers and radiologists blinded to the results of lab tests performed the imaging examinations.

In each patient, two radiologists, each blinded to the assessment of the other, calculated the aortic calcification score. The value included in the statistical analysis was the average of the two independent estimations.

The inflammation markers employed in our study were; C-reactive protein (CRP), fibrinogen, tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6).

The nutrition status was assessed by means of anthropometric (body mass index), biochemical (serum levels of albumin, cholesterol, and triglycerides, and diet related (normalized protein catabolic rate) parameters.

The vascular access was by tunneled cuffed catheters in 16 patients and by arteriovenous fistula in 35 patients. The primary kidney condition (responsible for the end-stage CKD leading to hemodialysis) was: adult type (dominant) polycystic kidney disease (in 5 patients), diabetic nephropathy secondary to type I diabetes mellitus (2 patients), diabetic nephropathy secondary to type II diabetes mellitus (8 patients), focal segmental glomerulosclerosis with nephrotic syndrome (1 patient), IgA nephropathy (1 patient), presumed (not histologically proven) glomerulonephritis (6 patients), congenital renal hypoplasia (1 patient), traumatic or surgical kidney loss (1 patient), drug-induced interstitial nephropathy (1 patient), pyelonephritis due to acquired obstructive uropathy (2 patients), kidney tumor (1 patient), renal vascular disease due to hypertension (21 patients), renal vascular disease due to polyarteritis nodosa (1 patient).

Statistical analysis

The correlations between two categorical parameters (such as LVDD and degenerative aortic stenosis) were assessed by means of Fisher's exact test. Chi-square test was also applied in the cases were none of the expected values was less than 5 (20). The correlations between one categorical parameter and one numerical parameter were assessed by Mann-Whitney test. Regression analysis was employed to assess the correlation between two numerical parameters, estimating the strength of the correlation by means of the correlation coefficient and the statistical significance of the correlation by means of t-statistic. R language and environment for statistical computing and graphics (version 4.1.2) was used to perform the statistical

computations. A *P* value equal to or less than 0.05 was considered as indicator of statistical significance.

Results

There were 32 patients with and 19 without LVDD. Table 1 is a summary of the demographic, biochemical, and imagistic features of our patients.

Associations between LVDD and inflammation- and oxidative stress-related parameters

Left ventricular diastolic dysfunction appears to have positive statistically significant correlations with serum CRP level (but not with others inflammation markers, such as fibrinogen, IL-6 and TNF-α) and with serum total antioxidant capacity (Figure 1 and Table 2). An intriguing negative statistically significant correlation was also found between LVDD and cortisol level (Table 2).

Associations between LVDD and demographic and metabolic parameters

There was no association between LVDD and age, but a tendency to association with male gender was obvious,

Table 1. Anthropometric, biochemical, radiological, and ultrasonographic features of the patients

Continuous parameters (real numbers)	LVDD present		LVDD absent	
	Mean ± SD	Median (q1 -q3)	Mean ± SD	Median (q1 -q3)
Age (years)	61.22 ± 13.59	61 (52.75-70.25)	57.32 ± 12.6	55 (49.5-67.5)
Body mass index (kg/m^2)	26.62 ± 5.81	25.9 (22.7-29.05)	27.37 ± 5.36	27 (24.2-29.45)
Total time on dialysis (months)	40 ± 22.69	41 (22.25-55.75)	42.05 ± 20.28	43 (31.5-59)
Hemoglobin (g/dL)	9.89 ± 1.48	10.1 (8.9-11.025)	9.87 ± 1.87	10.3 (8.25-11.15)
Daily urine output (mL)	439 ± 415	200 (162.5-1000)	642 ± 544	600 (200-950)
Ferritin (ng/mL)	994 ± 469	946 (598.5-1500)	871 ± 467	726 (558-1255)
Calcium (mg/dL)	8.37 ± 1.19	8.5 (7.8-9.125)	8.48 ± 0.62	8.6 (8.1-8.85)
Phosphorus (mg/dL)	5.34 ± 1.76	5 (3.9-6.7)	5.41 ± 1.55	5.1 (4.5-6.6)
Calcium× Phosphorus product (mg^2/dL^2)	44.36 ± 15.5	39.5 (33.4-57.6)	46.32 ± 15.21	40.2 (38.7-57.8)
Alkaline phosphatase (IU/L)	92.42 ± 64.53	68 (55-104.75)	84.63 ± 39.51	89 (48.5-101)
C reactive protein (mg/dL)	13.78 ± 24.34	5.7 (0.875-14.7)	3.47 ± 4.74	1.9 (0.1-4.7)
Fibrinogen (mg/dL)	398 ± 102	367 (328-426)	351 ± 57	364 (297-382)
Albumin (g/dL)	3.72 ± 0.58	3.8 (3.375-4.2)	3.91 ± 0.41	3.9 (3.65-4.3)
Cholesterol (mg/dL)	151.62 ± 40.95	140 (129.5-173.5)	164.47 ± 40.56	162 (144.5-171.5)
LDL-cholesterol (mg/dL)	84.44 ± 31.46	77.2 (63.5-97.65)	81.95 ± 19.82	87.8 (66.5-94.5)
Triglycerides (mg/dL)	127 ± 86	108 (63.5-150)	137 ± 45	142 (107-156.5)
Total protein (g/dL)	6.76 ± 0.61	6.75 (6.35-7.1)	6.83 ± 0.51	6.9 (6.6-7.1)
Uric acid (mg/dL)	6.3 ± 1.22	6.4 (5.575-7.125)	6.55 ± 1.35	6.3 (5.45-7.6)
Total antioxidant capacity (U/mL)	25.99 ± 4.51	26.2 (22.9-29.4)	23.14 ± 4.88	22 (20-26.6)
NADPH-oxidoreductase (ng/mL)	14.95 ± 2.98	16 (12.5-17.5)	14.31 ± 2.96	14.4 (12.1-16.3)
Xanthine-oxidase (ng/mL)	6.26 ± 0.44	6.2 (6-6.6)	6.45 ± 0.53	6.5 (5.95-6.9)
1,25-dihydroxyvitamin D (pg/mL)	316 ± 66	307 (265-378)	327 ± 47	339 (291-356.5)
Interleukin 6 (pg/mL)	6.97 ± 0.84	6.85 (6.575-7.45)	7.35 ± 1.27	7.3 (6.25-7.95)
Fibroblast growth factor 23 (pg/mL)	27.2 ± 3.37	27.95 (24.7-29.3)	27.08 ± 3.03	27.5 (24.1-29.3)
Tumor necrosis factor alpha (pg/mL)	8.12 ± 0.97	8.25 (7.325-8.9)	8.32 ± 0.98	8.2 (7.8-8.95)
Cortisol (µg/dL)	13.29 ± 3.9	13.4 (10-16)	15.89 ± 4.3	15.1 (12.5-19.5)
Dehydroepiandrosterone (µg/dL)	76.78 ± 67.06	52.2 (34.3-94.8)	124 ± 210	88 (49.2-100)
Gamma glutamyl transferase (U/L)	50.44 ± 58.7	23 (18-48.75)	35.53 ± 26.11	29 (20.5-43.5)
Parathormone (pg/mL)	177 ± 223	89.4 (36-191)	267 ± 284	139.4 (47-353)
Normalized protein catabolic rate	1.13 ± 0.34	1.1 (0.9-1.4)	1.26 ± 0.33	1.3 (1.1-1.45)
Intima-media thickness (mm)	0.61 ± 0.21	0.6 (0.5-0.7)	0.54 ± 0.1	0.5 (0.5-0.6)
Interventricular septum thickness (mm)	11.66 ± 1.91	12 (11-13)	9.63 ± 4.61	11 (10-12.5)

Table 1. Continued

Continuous parameters (integer numbers)	LVDD present		LVDD absent	
	Mean ± SD	Median (q1-q3)	Mean ± SD	Median (q1 -q3)
Aortic calcification total score	5.88 ± 5.72	4.5 (0.75-9)	2.16 ± 2.65	2 (0-3.5)
Number of carotid plaques	4.72 ± 4	4 (1.75-7.25)	3.58 ± 3.44	4 (0-5.5)
Number of femoral plaques	7.81 ± 4.21	>10 (3->10)	5.11 ± 5.26	2 (0->10)
Categorical parameters	**LVDD present**		**LVDD absent**	
	Yes (# patients)	No (# patients)	Yes (# patients)	No (# patients)
Male gender	22	10	8	11
Obesity	8	24	5	14
Overweight	16	16	13	6
Underweight	1	31	1	18
Carotid plaques	27	5	15	4
Femoral plaques	31	1	14	5
Aortic annulus calcifications	18	14	4	15
Aortic valve calcifications	19	13	6	13
Aortic valve/annulus calcifications	23	9	8	11
Degenerative aortic stenosis	7	25	0	19
Degenerative aortic regurgitation	6	26	2	17
Mitral valve calcifications	19	13	5	14
Mitral regurgitation	13	19	6	13
Pulmonary hypertension	5	27	1	18

LVDD, left ventricular diastolic dysfunction; SD, standard deviation; q1/q3, first/third quartile; #patients, number of patients.

although the result did not reach statistical significance as computed by chi square test (a chi-square statistic of 3.4943, corresponding to a *P* value of 0.06).

No association was found between LVDD and metabolic/nutrition parameters, including body mass index, obesity, overweight, underweight, albumin, cholesterol, triglycerides, calcium, phosphorus, calcium × phosphorus product, vitamin D, parathormone, hemoglobin and ferritin.

Associations between LVDD and imaging atherosclerosis markers

Mann-Whitney U test uncovered a correlation between LVDD and arterial atherosclerosis burden as reflected by

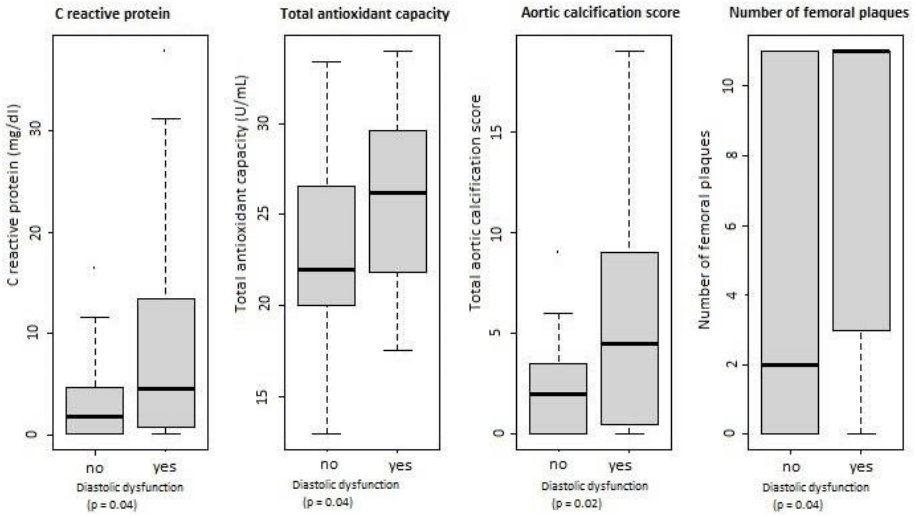

Figure 1. Associations between left ventricular diastolic dysfunction and inflammation, oxidative stress, number of femoral plaques, and the aortic calcification score. *P* values were calculated by means of Mann-Whitney U test.

Table 2. Associations between left ventricular diastolic dysfunction (categorical parameter) and inflammation and oxidative stress related parameters (numerical parameter) assessed by Mann-Whitney U test

Numerical parameter	LVDD		W statistic	*P* value
	Present median (q1-q3)	Absent median (q1-q3)		
CRP (mg/dL)	5.7 (0.875-14.7)	1.9 (0.1-4.7)	409.5	0.04
Total antioxidant capacity (U/mL)	26.2 (21.875-29.425)	22 (20-26.6)	410	0.04
Cortisol (µg/dL)	13.4 (10.025-15.975)	15.1 (12.5-19.5)	201.5	0.05
Number of femoral plaques	>10 (3->10)	2 (0->10)	401	0.04
Aortic calcification score	4.5 (0.75-9)	2 (0-3.5)	425	0.02

CRP, C-reactive protein; LVDD, left ventricular diastolic dysfunction; q1, 1st quartile 1; q3, 3rd quartile.

the number of femoral plaques and the aortic calcification score (Table 3 and Figure 1).

Fisher's exact test revealed associations between LVDD and most of the imaging atherosclerosis markers (but for aortic valve calcifications and carotid plaques) (Table 3). There was no association between LVDD and aortic or mitral valve regurgitation or pulmonary hypertension.

The most obvious putative confounder is degenerative aortic stenosis which by itself engenders LVDD (via the LVH it induces (21)) and is expected to be correlated with degenerative changes in other cardiac and arterial structures as CKD induces widespread valvular and arterial calcifications (22). All our patients with aortic valve stenosis also had LVDD. Therefore, the statistical computations needed to be repeated after eliminating this possible confounder, i.e. after eliminating the seven patients with aortic stenosis. Among the 44 remaining patients, 25 have LVDD and 19 have not. The only associations that remained statistically significant were those of LVDD with serum total antioxidant capacity, cortisol level, and aortic calcification score (Table 4). The tendency to association also with CRP is clear (compare the medians and third quartiles), but it narrowly fails to reach statistical significance, probably due to the smallness of the sample.

None of the associations between LVDD and IAMs (presence of femoral plaques, of aortic annulus calcifications, and of mitral valve calcifications) remained statistically significant after removing the seven patients with aortic stenosis.

Discussion

Although multiple mechanisms have been identified explaining myocardial hypertrophy and fibrosis underlying LVDD in hemodialysis patients (5), the biochemical and imaging associations relevant for clinical practice have been less explored. Our study, aimed at contributing to this under researched area, revealed some data concordant with what is already known, but also some differences.

The statistical analysis of our data indicated that in hemodialysis patients there is an association between LVDD and inflammation, as reflected by CRP, which is in agreement with the association between LVDD and high-sensitivity CRP (hs-CRP) in CKD patients demonstrated

Table 3. Results of the Fisher's exact test for the association between left ventricular diastolic dysfunction and imaging atherosclerosis markers

IAM	DD+IAM+	DD+IAM-	DD-IAM+	DD-IAM-	*P* value	Odds ratio
Femoral plaques	31	1	14	5	0.022	10.54
Aortic valve stenosis	7	25	0	19	0.037	Infinite
Aortic annulus calcifications	18	14	4	15	0.02	4.67
Aortic valve/annulus calcifications	23	9	8	11	0.044	3.42
Aortic valve calcifications	19	13	6	13	0.083	3.09
Mitral valve calcifications	19	13	5	14	0.041	3.98

DD, diastolic dysfunction; IAM, imaging atherosclerosis marker.
The columns 2-5 contain the number of patients in the four categories: diastolic dysfunction present with positive IAM (DD+IAM+), diastolic dysfunction present with negative IAM (DD+IAM+), diastolic dysfunction absent with positive IAM (DD-IAM+), diastolic dysfunction absent with negative IAM (DD-IAM-).

Table 4. Associations between left ventricular diastolic dysfunction (categorical parameter) and inflammation and oxidative stress related parameters (numerical parameter) assessed by Mann-Whitney test

Numerical parameter	LVDD		W statistic	*P* value
	Present median (q1-q3)	Absent median (q1-q3)		
CRP (mg/dL)	5.4 (0.9-14.5)	1.9 (0.1-4.7)	161	0.07
Total antioxidant capacity (U/mL)	26.6 (21.9-30.1)	22 (20-26.6)	148.5	0.04
Cortisol (µg/dL)	14 (9.8-16.5)	15.1 (12.5-19.5)	323	0.04
Number of femoral plaques	9 (3->10)	2 (0->10)	179	0.1
Aortic calcification score	4 (1-9)	2 (0-3.5)	143.5	0.02

CRP, C-reactive protein; LVDD, left ventricular diastolic dysfunction; q1, 1st quartile 1; q3, 3rd quartile.

by other researchers (1), and is at least partially explained by the correlation between LVH and CRP in pre-dialysis patients (9) and in patients on hemodialysis (10) and with hs-CRP in hemodialysis patients (23), hs-CRP being an independent predictor for LVH in CKD (11). However, we found no correlation between LVDD and other inflammatory markers, such as IL-6 and TNF-α (in agreement with previous studies on CKD patients (1)), although other researchers demonstrated that LVH is associated with TNF-α in CKD patients (11) and in hemodialysis patients (23) and with IL-6 in CKD patients (1) and in hemodialysis patients (23).

The association of LVDD with oxidative stress demonstrated by our study is concordant with the findings of other researchers linking diastolic function to overproduction of ROS due to the involvement of oxidative stress in promoting cardiac remodeling (5) in CKD patients.

Our study failed to demonstrate a relation between LVDD and anemia, although there are studies suggesting that in CKD patients anemia is correlated with cardiac hypertrophy (24) and with left ventricular dilatation and heart failure (25).

We did not find an association between LVDD and disorders of bone and mineral metabolism, although other studies demonstrated that in hemodialysis patients LVDD is correlated with serum phosphorus level and calcium × phosphate product (13), while LVH is associated with serum PTH (13), phosphorus, and calcium level (13), and with vitamin D deficiency (16). Interestingly, in uremic rats cardiac fibrosis is associated with high serum parathormone level (15) and with hyperphosphatemia (14).

Conclusion

LVDD is positively correlated with inflammation and oxidative stress markers and with the severity of aortic calcification. The association of LVDD with valvular and peripheral arterial calcifications / atherosclerosis is largely mediated by its association with degenerative aortic stenosis. The purpose of designing therapeutic strategies is to prevent or slow the course of LVDD, thereby influencing the cardiovascular and general outcomes of these patients.

Limitations of the study

The most important limitations of this study are; 1. The relatively low number of enrolled patients. 2. The time interval the imaging investigation lagged behind the performance of laboratory tests; however, this delay was unavoidable given the ultrasound examination, as a human-dependent investigation, is inherently more labor- and time-intensive than laboratory tests, which are machine-dependent. 3. The putative confounders, among which degenerative aortic stenosis was probably the most important; the elimination of this confounding factor resulted in an even smaller sample of patients on which to base our conclusions. Studies on larger samples are necessary to identify the biochemical correlates/markers/determinants of LVDD in hemodialysis patients.

Authors' contribution

Conceptualization: DD, DT, AEBS, MMM and DI.
Methodology: DD, DT, MMM and DI.
Validation: DD, DT, AEBS, MIG, MMM, IAV and DI.
Formal analysis: DD, DT, AEBS, MMM and DI.
Investigation: DD, DT, AEBS and MMM.
Resources: DD, DT, AEBS and DI.
Data curation: DD, DT and MMM.
Writing—original draft preparation: DD, DT, AEBS, MIG, MMM and DI.
Writing—review and editing: DD, DT, AEBS, MMM and DI.
Visualization: DD and DT.
Supervision: DD, DT and DI.
Project administration: DD, DT and DI.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of University Emergency Hospital Bucharest approved this study. Accordingly, written informed consent was taken from all participants.

Funding/Support

None.

References

1. Gupta J, Dominic EA, Fink JC, Ojo AO, Barrows IR, Reilly MP, et al; CRIC Study Investigators. Association between Inflammation and Cardiac Geometry in Chronic Kidney Disease: Findings from the CRIC Study. PLoS One. 2015;10:e0124772. doi: 10.1371/journal.pone.0124772.
2. Escoli R, Carvalho MJ, Cabrita A, Rodrigues A. Diastolic Dysfunction, an Underestimated New Challenge in Dialysis. Ther Apher Dial. 2019;23:108-117. doi: 10.1111/1744-9987.12756.
3. Díez J, Laviades C. La cardiopatía hipertensiva en el paciente con enfermedad renal crónica [Hypertensive heart disease in the patient with chronic kidney disease]. Nefrologia. 2008;28:135-42. [Spanish].
4. Nardi E, Mulè G, Giammanco A, Mattina A, Geraci G, Nardi C, et al. Left ventricular hypertrophy in chronic kidney disease: A diagnostic criteria comparison. Nutr Metab Cardiovasc Dis. 2021;31:137-144. doi: 10.1016/j.numecd.2020.08.028.
5. Kaesler N, Babler A, Floege J, Kramann R. Cardiac Remodeling in Chronic Kidney Disease. Toxins (Basel). 2020;12:161. doi: 10.3390/toxins12030161.
6. Pecoits-Filho R, Bucharles S, Barberato SH. Diastolic heart failure in dialysis patients: mechanisms, diagnostic approach, and treatment. Semin Dial. 2012;25:35-41. doi: 10.1111/j.1525-139X.2011.01011.x.
7. Benz K, Hilgers KF, Daniel C, Amann K. Vascular Calcification in Chronic Kidney Disease: The Role of Inflammation. Int J Nephrol. 2018;2018:4310379. doi: 10.1155/2018/4310379.
8. Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C. Left Ventricular Hypertrophy in Chronic Kidney Disease Patients: From Pathophysiology to Treatment. Cardiorenal Med. 2015;5:254-66. doi: 10.1159/000435838.
9. Ortega O, Gallar P, Muñoz M, Rodríguez I, Carreño A, Ortiz M, et al. Association between C-reactive protein levels and N-terminal pro-B-type natriuretic peptide in pre-dialysis patients. Nephron Clin Pract. 2004;97:c125-30. doi: 10.1159/000079170.
10. Kim BS, Jeon DS, Shin MJ, Kim YO, Song HC, Lee SH, et al. Persistent elevation of C-reactive protein may predict cardiac hypertrophy and dysfunction in patients maintained on hemodialysis. Am J Nephrol. 2005;25:189-95. doi: 10.1159/000085585.
11. Cottone S, Nardi E, Mulè G, Vadalà A, Lorito MC, Riccobene R, et al. Association between biomarkers of inflammation and left ventricular hypertrophy in moderate chronic kidney disease. Clin Nephrol. 2007;67:209-16. doi: 10.5414/cnp67209.
12. Hazin MAA. Anemia in chronic kidney disease. Rev Assoc Med Bras (1992). 2020;66:s55-s58. doi: 10.1590/1806-9282.66.S1.55.
13. Strózecki P, Adamowicz A, Nartowicz E, Odrowaz-Sypniewska G, Włodarczyk Z, Manitius J. Parathormon, calcium, phosphorus, and left ventricular structure and function in normotensive hemodialysis patients. Ren Fail. 2001;23:115-26. doi: 10.1081/jdi-100001291.
14. Amann K, Törnig J, Kugel B, Gross ML, Tyralla K, El-Shakmak A, et al. Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia. Kidney Int. 2003;63:1296-301. doi: 10.1046/j.1523-1755.2003.00864.x.
15. Amann K, Ritz E, Wiest G, Klaus G, Mall G. A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol. 1994;4:1814-9. doi: 10.1681/ASN.V4101814.
16. Bucharles S, Barberato SH, Stinghen AE, Gruber B, Meister H, Mehl A, et al. Hypovitaminosis D is associated with systemic inflammation and concentric myocardial geometric pattern in hemodialysis patients with low iPTH levels. Nephron Clin Pract. 2011;118:c384-91. doi: 10.1159/000323664.
17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277-314. doi: 10.1016/j.echo.2016.01.011.
18. Prasad SB, Holland DJ, Atherton JJ, Whalley G. New Diastology Guidelines: Evolution, Validation and Impact on Clinical Practice. Heart Lung Circ. 2019;28:1411-20. doi: 10.1016/j.hlc.2019.03.013.
19. Kauppila LI, Polak JF, Cupples LA, Hannan MT, Kiel DP, Wilson PW. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis. 1997;132:245-50. doi: 10.1016/s0021-9150(97)00106-8.
20. Yates D, Moore D, McCabe G. The Practice of Statistics. 1st ed. Freeman WH, editor. New York; 1999. p. 734.
21. Sobczak S, Sakowicz A, Pietrucha T, Lelonek M. Diagnostic utility of biomarkers of left ventricular stress in patients with aortic stenosis and preserved left ventricular ejection fraction. Kardiochir Torakochirurgia Pol. 2017;14(2):93-98. doi: 10.5114/kitp.2017.68737.
22. Ureña-Torres P, D'Marco L, Raggi P, García-Moll X, Brandenburg V, Mazzaferro S, et al. Valvular heart disease and calcification in CKD: more common than appreciated.

Nephrol Dial Transplant. 2020;35:2046-2053. doi: 10.1093/ndt/gfz133.
23. Shi L, Song J, Zhang X, Li Y, Li H. Correlation between the microinflammatory state and left ventricular structural and functional changes in maintenance haemodialysis patients. Exp Ther Med. 2013;6:532-536. doi: 10.3892/etm.2013.1131.
24. Silberberg JS, Rahal DP, Patton DR, Sniderman AD. Role of anemia in the pathogenesis of left ventricular hypertrophy in end-stage renal disease. Am J Cardiol. 1989;64:222-4. doi: 10.1016/0002-9149(89)90462-1.
25. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis. 1996;28:53-61. doi: 10.1016/s0272-6386(96)90130-4.