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The mediating role of the left ventricular mass index on the relationship between the fluid balance and left ventricular diastolic function in patients with chronic kidney disease

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Background: The pathophysiological mechanism of cardiovascular disease in patients with chronic kidney disease (CKD) is complicated. Mediation analysis is an important statistical tool for gaining insight into the complex mechanisms of exposure-outcome effects. We investigated the potential mediating role of the left ventricular mass index (LVMI) on the association between fluid balance (overhydration/extracellular water, OH/ECW) and left ventricular diastolic function (E/e´ ratio) in patients with CKD not yet on dialysis.
Methods: Bioimpedance spectroscopy, echocardiography, and laboratory evaluations were performed on 425 consecutive patients on the same day. The patients were classified into two groups according to the estimated glomerular filtration rate corresponding to CKD stages 3 and 5. Mediation analysis was performed using the PROCESS macro and bootstrapping methods.
Results: OH/ECW and LVMI were positively correlated with the E/e´ ratio in both the CKD stages 3 and five groups. In CKD stage 5, there was a statistically significant association between OH/ECW and LVMI, whereas no correlation was observed in CKD stage 3. In the mediation analysis, LVMI positively mediated the relationship between OH/ECW and E/e´ ratio when controlling for confounders in patients with CKD stage 5 (B = 2.602; Boot 95% confidence interval, 1.313–4.076).
Conclusion: In our analysis, the indirect effect of mediators was significant in patients with advanced CKD. Therefore, our study suggests that further research on several other risk factors may be needed to determine the underlying mechanisms of association between the associated factors in all CKD stages.

Keywords: Chronic kidney diseases, Diastole, Fluid balance, Impedance, Left ventricular hypertrophy

Introduction

Cardiovascular disease is the leading cause of death and hospitalization in patients with chronic kidney disease (CKD), regardless of the cause. Structural and functional myocardial abnormalities are common in patients with CKD because of high blood pressure, fluid overload, and nontraditional risk factors associated with CKD. The myocardial mass represented by left ventricular (LV) mass to body surface area (BSA) index (LV mass index, LVMI) is

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one of the sensitive indicators of cardiac structural changes [1]. LV diastolic dysfunction (LVDD), represented by mitral peak Doppler E-wave to peak mitral annulus velocity ratio (E/e´ ratio), is a commonly observed functional impairment [2].

Although both changes are commonly associated with poor outcomes in patients with end-stage kidney disease (ESKD) [2–4], the clinical characteristics of LV hypertrophy (LVH) and LVDD in CKD differ depending on the CKD stage [5,6]. In patients with CKD, the mechanism of LVDD is complex and is mainly associated with LVH, which is a physiological response to pressure and volume overloads. In a longitudinal observational study, patients with more advanced CKD showed greater increases in LV mass and volume than those with early-stage CKD. Additionally, cardiac remodeling did not affect LV systolic function, whereas LVDD was aggravated in progressive CKD [7].

Euvolemia in patients with renal insufficiency from the early to late stages is important not only for short-term fluid management but also for the long-term prevention of cardiovascular disease; this is because fluid overload is a predictor of mortality and morbidity [8]. Although the relationship between fluid overload and cardiac impairment is complex, fluid overload is a critical step in the pathophysiological pathway of congestive heart failure in patients with ESKD. In general, LVH and LVDD are known to precipitate and/or cause heart failure [9]. Most previous studies on structural and functional abnormalities of the heart related to fluid overload have focused on patients on dialysis, and relatively few studies have focused on patients with CKD. We previously reported that biomarkers reflecting LVH and LVDD are associated with fluid overload in patients with CKD [10,11].

During the CKD progression course, fluid imbalance, which may be related to hemodynamics and structural and functional changes in the heart, can occur and evolve in complex patterns, either individually or simultaneously. Nevertheless, most of the studies, just like what we have analyzed before, have investigated a single relationship between fluid balance and cardiac structural and functional impairments, or have evaluated the degree of influence of single factors on the relationships. Analysis in this manner implies a limitation in that the role of multiple parameters cannot be adequately explained. The mediation effect represents the influence of the predictor on the dependent variable through the mediator [12]. The causal structure behind the relationship between the predictor and dependent variables can be understood using the statistics of the mediating effect analysis. With this theoretical background in mind, we investigated the potential mediating role of LV mass in the association between fluid balance and LV diastolic function in patients with CKD.

Methods

Patients and data collection

Since 2014, we registered consecutive patients with CKD in a bioimpedance cohort after receiving approval (No. CR319143 for CKD stage 3 and No. CR316024 for CKD stage 5) from the Institutional Review Board of Yonsei University Wonju Severance Christian Hospital. Using the estimated glomerular filtration rate (eGFR), patients with CKD stages 3 and 5 were analyzed. All patients underwent simultaneous bioimpedance spectroscopy (BIS), echocardiography, and laboratory evaluation at the time of enrolment. The CKD stage 5 group consisted of dialysis-naïve patients only. This means that all the aforementioned tests were performed prior to the initiation of renal replacement therapy in patients with CKD stage 5. Therefore, our study was a retrospective observational analysis of a prospective cohort database of patients with stages 3 and 5 CKD. All patients provided written informed consent before participating in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Conventional echocardiographic study

Echocardiography was performed in harmonic imaging mode using a 3-MHz transducer and a commercial ultrasound system (GE Vivid E9; GE Healthcare). LV mass was calculated following the American Society of Echocardiography recommendations [13] using the following equation:

$$LV\ mass = 0.8 \times [1.04 \times \{(IVS + L\ VID + PWT)^3 - (LVID)^3\}] + 0.6\ g$$

where *IVS* is the interventricular septum, *LVID* is the LV internal diameter, and *PWT* is inferolateral wall thickness. All measurements were performed at end-diastole. To correct for BSA, LVMI was calculated by dividing LV mass by BSA

using the following formula: $BSA = (0.007184 \times weight^{0.425} \times height^{0.725})\ m^2$. Transmitral inflow velocities were measured using pulsed-wave Doppler in the apical four-chamber view, with the sample volume placed at the mitral valve leaflet tips. Transmitral early diastolic (E-wave) velocities were measured. Tissue Doppler imaging in the apical four-chamber view was used to measure LV myocardial velocities with the sample volume placed at the septal mitral annulus. We measured the peak early (e′) diastolic mitr al annular velocity and calculated the E/e′ r atio [14]. The left atrial volume index (LAVI), LV end-diastolic volume (LVEDV), and LV ejection fraction were measured according to previously mentioned recommendations. Echocardiography was performed by trained cardiologists who were blinded to the patient's information.

Assessment of the volume status

Whole-body BIS was performed using BCM (Body Composition Monitoring; Fresenius Medical Care AG & Co.). The BCM utilizes alternating electric currents across 50 discrete frequencies covering the frequency spectrum from 5 to 1,000 kHz and measures the impedance of each current. Disposable electrode patches placed on the wrist and ankle were used for all the measurements. The validity of BIS in the general and dialysis populations has been demonstrated in comparison to gold standard methods. Extracellular water (ECW), intracellular water, and total body water were automatically provided by the BCM using the equations of Moissl et al. [15] based on the Hanai mixture theory adjusted for body mass index (BMI). A three-compartment BIS model separates body weight into normally hydrated lean tissue mass, normally hydrated adipose tissue mass, and fluid overload, which is commonly described as the overhydration (OH) compartment [16]. Extracellular fluid overload, presented as positive or negative OH, can be calculated from the difference between the actual measured ECW and the expected ECW [17]. Because specific OH values vary in clinical relevance according to the patient body size, OH/ECW was primarily used to determine the volume status as relative OH in our study. In the same context, the patient's BMI was recalculated using the following formula: $corrected\ BMI\ (cBMI,\ kg/m^2) = (body\ weight - OH)/height^2$.

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables are reported as means with standard deviations. Based on the eGFR, all patients were divided into two groups: CKD stage 3 and CKD stage 5. Patient characteristics between groups were tested using a chi-square test and a two-sample t test, as appropriate. Pearson correlation analysis was used to examine correlations between the E/e´ ratio and other variables, such as laboratory findings, echocardiographic parameters, and markers of volume status in each group. Statistical analyses were performed using the IBM SPSS version 25.0 (IBM Corp.). Statistical significance was defined as $p < 0.05$.

Finally, mediation analysis was performed using the PROCESS macro and bootstrapping for SPSS (PROCESS version 4.1; Andrew F. Hayes) [18]. The bootstrap test complements the limited ability of the Sobel test, which relies on the assumption of normality [19,20]. The statistical significance of the mediating effect was determined using the confidence intervals (CI) of bootstrapping estimation techniques; when 0 was included in the bootstrap 95% CI, the indirect effect was considered nonsignificant. Recently, this method has been recommended more than Baron and Kenny's method [12], which requires the Sobel test [19] to verify the indirect effect of the mediation analysis. Therefore, in this study, bootstrap analyses were used to verify the significance of the indirect effect of LVMI on the relationship between OH/ECW and E/e´ ratio in each group. A total of 5,000 bootstrap samples were repeatedly extracted to estimate the indirect effect, adjusted for age, sex, diabetes prevalence, cBMI, and eGFR. Graphs were generated using the Prism software (version 5.02; GraphPad Software).

Results

Characteristics of the study patients

The clinical characteristics of both groups according to the CKD stage are presented in Tables 1, 2 and Fig. 1. The mean ages of male and female patients were 60.80 ± 12.92 years and 61.09 ± 13.60 years, respectively. Males accounted for 263 patients (61.9%). There was no statistical difference in the E/e´ ratio, LVMI, and OH/ECW between men and

Table 1. Comparison of demographics, volume status, echocardiographic findings, and serum chemistry between patients with CKD stage 3 and 5

Variable	Total	CKD stage 3	CKD stage 5	p-value
No. of patients	425	83	342	
Age (yr)	60.91 ± 13.17	61.86 ± 11.92	60.68 ± 13.47	0.468
Sex				0.007
Male	263 (61.9)	62 (23.6)	201 (76.4)	
Female	162 (38.1)	21 (13.0)	141 (87.0)	
Diabetes				0.09
Yes	255 (60.0)	43 (16.9)	212 (83.1)	
No	170 (40.0)	40 (23.5)	130 (76.5)	
SBP (mmHg)	140.56 ± 19.06	130.89 ± 15.39	142.91 ± 19.14	<0.001
DBP (mmHg)	79.20 ± 12.00	75.48 ± 12.55	80.10 ± 11.10	0.002
Body weight (kg)	66.51 ± 12.63	71.61 ± 13.43	65.27 ± 12.09	<0.001
cBMI (kg/m^2)	24.27 ± 4.13	26.30 ± 3.93	23.78 ± 4.03	<0.001
OH/ECW (%)	12.87 ± 14.65	2.87 ± 6.60	15.29 ± 15.03	<0.001
LAVI (mL/m^2)	39.22 ± 12.18	27.02 ± 7.77	39.70 ± 11.76	<0.001
LVEDV (mL)	142.62 ± 35.02	126.67 ± 30.68	146.49 ± 34.95	<0.001
E/e´ ratio	14.65 ± 5.56	11.72 ± 3.91	15.36 ± 5.67	<0.001
LVMI (g/m^2)	110.62 ± 29.92	89.80 ± 24.09	115.67 ± 29.03	<0.001
LVEF (%)	61.27 ± 7.56	62.78 ± 4.56	60.90 ± 8.09	0.005
Hemoglobin (g/dL)	9.90 ± 2.20	13.38 ± 1.72	9.06 ± 1.28	<0.001
tCO_2 (mmol/L)	19.34 ± 4.70	25.64 ± 3.24	17.81 ± 3.74	<0.001
Total protein (g/dL)	6.30 ± 0.85	7.20 ± 0.51	6.08 ± 0.77	<0.001
Albumin (g/dL)	3.65 ± 0.61	4.36 ± 0.36	3.48 ± 0.54	0.83
Total cholesterol (mg/dL)	148.70 ± 44.07	162.01 ± 35.34	145.47 ± 45.40	0.002
Triglyceride (mg/dL)	138.91 ± 76.97	175.37 ± 87.97	130.06 ± 71.43	<0.001
HDL-C (mg/dL)	40.05 ± 13.30	46.52 ± 13.44	38.47 ± 12.80	<0.001
LDL-C (mg/dL)	81.34 ± 36.99	79.84 ± 30.00	81.71 ± 38.53	0.68
Alkaline phosphatase (U/L)	81.33 ± 38.93	76.98 ± 32.09	82.40 ± 40.39	0.26
Calcium (mg/dL)	8.01 ± 1.17	9.39 ± 0.40	7.68 ± 1.04	<0.001
Phosphate (mg/dL)	5.45 ± 1.83	3.27 ± 0.50	5.98 ± 1.63	<0.001
Uric acid (mg/dL)	7.59 ± 2.37	6.77 ± 1.83	7.79 ± 2.45	<0.001
eGFR (mL/min/1.73 m^2)	14.18 ± 15.38	44.34 ± 7.10	6.85 ± 2.60	<0.001

Data are expressed as number only, mean ± standard deviation, or number (%).
cBMI, corrected body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; ECW, extracellular water; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; OH, overhydration; SBP, systolic blood pressure; tCO_2, total carbon dioxide.

women with CKD stage 3. In CKD stage 5, LVMI and OH/ECW were not significantly different between men and women, whereas the E/e´ ratio (14.55 ± 5.10 vs. 16.52 ± 6.24, p = 0.002) was significantly higher in women.

Although the OH/ECW (5.54% ± 6.45% vs. 0.00% ± 5.54%, p < 0.001) of the diabetic patients was higher than that of the nondiabetic patients with CKD stage 3, E/e´ ratio and LVMI were not different. In CKD stage 5, E/e´ ratio (16.28 ± 5.60 vs. 13.86 ± 5.49, p < 0.001) and OH/ECW (18.56% ± 14.81% vs. 9.96% ± 13.87%, p < 0.001) were significantly greater in patients with diabetes compared to those patients without, while LVMI was not different. In our study, fluid overload, defined as an OH/ECW greater than 15% [21], was present in six patients (6.0%) with CKD stage 3, whereas 152 patients (44.4%) presented with CKD stage 5. Meanwhile, LVDD with an E/e´ ratio >15 was present in

Table 2. Correlation of E/e´ ratio with variables in each group

Variable	Total		CKD stage 3		CKD stage 5	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
Age	0.193	<0.001	0.129	0.24	0.222	<0.001
SBP	0.219	<0.001	0.050	0.66	0.181	0.001
DBP	0.019	0.69	−0.035	0.75	−0.067	0.21
Body weight	−0.076	0.12	0.040	0.72	−0.039	0.47
cBMI	−0.019	0.70	0.160	0.15	0.030	0.58
OH/ECW	0.348	<0.001	0.312	0.004	0.286	<0.001
LAVI	0.498	<0.001	0.275	0.01	0.463	<0.001
LVEDV	0.272	<0.001	0.262	0.02	0.223	<0.001
LVMI	0.402	<0.001	0.363	0.001	0.343	<0.001
LVEF	−0.255	<0.001	−0.090	0.42	−0.254	<0.001
Hemoglobin	−0.289	<0.001	−0.204	0.06	−0.135	0.01
tCO_2	−0.251	<0.001	−0.036	0.74	−0.117	0.03
Total protein	−0.236	<0.001	−0.084	0.45	−0.127	0.02
Albumin	−0.283	<0.001	−0.163	0.14	−0.172	0.001
Total cholesterol	−0.027	0.58	−0.077	0.49	0.024	0.78
Triglyceride	−0.109	0.02	−0.068	0.54	0.112	0.66
HDL-C	−0.067	0.18	−0.049	0.66	0.002	0.97
LDL-C	0.042	0.39	−0.014	0.90	0.045	0.41
Alkaline phosphatase	0.042	0.39	0.074	0.51	0.023	0.67
Calcium	−0.279	<0.001	−0.140	0.21	−0.166	0.002
Phosphate	0.252	<0.001	0.193	0.08	0.126	0.02
Uric acid	0.141	0.004	0.045	0.69	0.109	0.049
eGFR	−0.268	<0.001	0.027	0.81	−0.133	0.01

cBMI, corrected body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; ECW, extracellular water; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; OH, overhydration; SBP, systolic blood pressure; tCO_2, total carbon dioxide.

nine patients (10.8%) with CKD stage 3. Among patients with CKD stage 5, 144 (42.1%) had LVDD.

Correlation of volume status, echocardiographic findings, and serum chemistry with E/e´ ratio

In all patients, LVMI and OH/ECW were positively correlated with E/e´ ratio (Table 2). LAVI and LVEDV were also positively associated with the E/e´ ratio. However, no consistent correlation was observed for the other measured variables compared to the other groups. To perform mediation analysis (Fig. 2), it is first necessary to show significant correlations between predictor and mediator, between predictor and dependent variable, and between mediator and dependent variable. The dependent variable was the E/e´ ratio. Predictors and mediators were OH/ECW and LVMI, respectively. In our analysis, the three criteria for significant correlations were not fulfilled in patients with CKD stage 3. OH/ECW was not significantly associated with LVMI ($p = 0.06$). However, OH/ECW was positively associated with LVMI ($r = 0.229$, $p < 0.001$) in patients with CKD stage 5.

Mediating effect of left ventricular mass index

The indirect effect for all patients with CKD was statistically significant because 0 was not included in the bootstrap 95% CI (B = 2.980; Boot 95% CI, 1.729–4.416). However, there were no consistent findings in the subgroup analysis. This was statistically significant only in CKD stage 5. LVMI

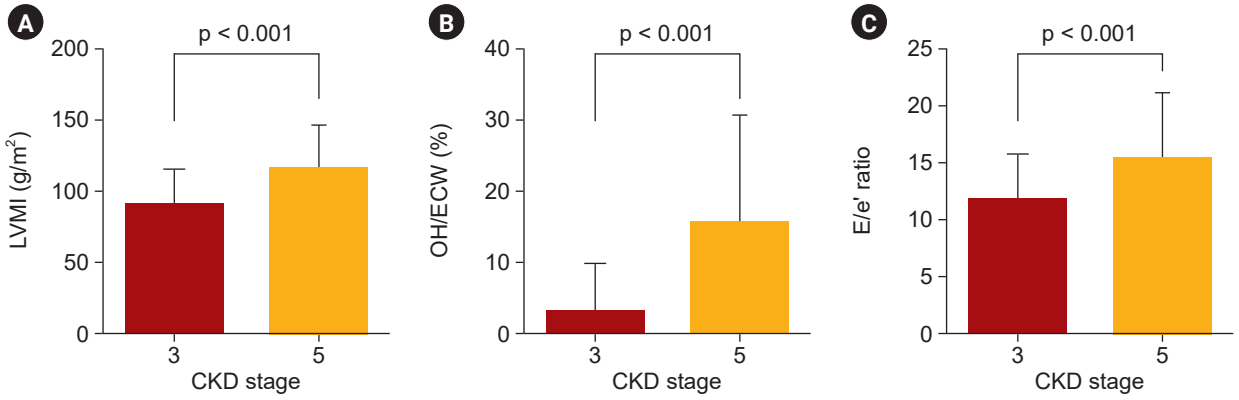

Figure 1. Two-sample t test findings between CKD stages 3 and 5. (A) Left ventricular mass index (LVMI). (B) Overhydration to extracellular water (OH/ECW). (C) E/e´ ratio.
CKD, chronic kidney disease.

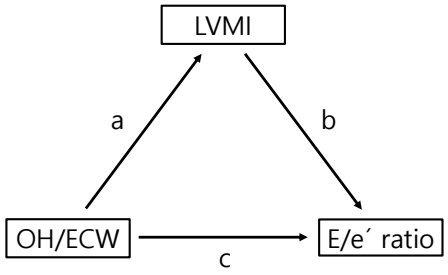

Figure 2. Path diagram of a single mediator model.
ECW, extracellular water; LVMI, left ventricular mass index; OH, overhydration.

mediated the relationship between OH/ECW and E/e´ ratio even after controlling for age, sex, diabetes prevalence, cBMI, and eGFR (B = 2.602; Boot 95% CI, 1.313–4.076). The indirect effect of LVMI on CKD stage 3 was not significant (B = 4.841; Boot 95% CI, –0.0002 to 11.435). Table 3 presents the results of the mediation analysis for each group.

Discussion

In patients with CKD, LVDD and LVH are common and are closely related to increased cardiovascular mortality. In the general population, LVH which is a physiological response to pressure overload has been reported as one of the pathogenetic mechanisms of LVDD. However, it is not clear whether cardiac structural changes occur prior to functional changes in CKD or vice versa. Previous studies have shown different results depending on the CKD stage at the time of evaluation and the evaluation tools used, such as echocardiography and cardiac magnetic resonance [22–24]. Certain pathophysiological factors may have different degrees of impact on the occurrence and exacerbation of cardiac structural and functional abnormalities at different stages of CKD, regardless of traditional or nontraditional CKD-related factors.

Fluid balance is particularly important because it can promote hemodynamic stability and minimize cardiovascular complications in patients with CKD. Fluid overload is associated with cardiovascular mortality and may be a relevant target for improving outcomes in patients undergoing hemodialysis [25]. Previous studies on the link between cardiac abnormalities and fluid imbalance have mostly focused on patients with ESKD undergoing dialysis [26]. As an extension of this point, fluid overload in patients with CKD is the same factor [8]. However, to prevent cardiovascular complications, it is essential to consider several factors rather than finding and controlling only one factor.

It is well known that the prevalence of LVH increases as kidney function decreases [27]. It is not yet clear which one plays a more important role in the development of LVH at each stage of CKD, making it difficult to generalize its evolution in CKD. Therefore, compared to the pathophysiology in the general population, the pathophysiology of LVH in patients with CKD is very complicated. In patients with advanced CKD, fluid overload has also been reported as a risk factor for LVH [11,28,29]. If the heart loses its elasticity as a result of thickened heart walls and is unable to pump as much force as necessary, fluid overload may fur-

Table 3. Bootstrapping results with confidence intervals for the lower and upper limits

Group	Effect	Label	Estimate	SE	95% confidence interval	
					LLCI	ULCI
CKD stage 3 and 5	Indirect (Booted)	a × b	2.980	0.680[a]	1.729[a]	4.416[a]
	Direct	c	10.268	1.893	6.547	13.988
	Total	c + (a × b)	13.248	1.963	9.461	17.035
CKD stage 3	Indirect (Booted)	a × b	4.841	2.961[a]	−0.0002[a]	11.435[a]
	Direct	c	18.469	6.874	4.776	32.161
	Total	c + (a × b)	23.310	7.064	9.241	37.374
CKD stage 5	Indirect (Booted)	a × b	2.602	0.713[a]	1.313[a]	4.076[a]
	Direct	c	9.563	2.054	5.523	13.603
	Total	c + (a × b)	12.165	2.085	8.064	16.266

Covariates included age, sex, diabetes prevalence, corrected body mass index, and estimated glomerular filtration rate.
CKD, chronic kidney disease; LLCI, lower limit confidence interval; SE, standard error; ULCI, upper limit confidence interval.
[a]Bootstrapping results with standard error and 95% confidence intervals for the lower and upper limits.

ther accelerate heart failure at any stage of CKD. Although the pathogenesis of LVDD is complex, the clinical course and patterns of LVDD are also determined by the CKD stage. LVDD can be caused by various other factors, with or without LVH. Among them, fluid overload acts as an independent risk factor for LVDD and as a promoting factor for heart failure with preserved ejection fraction in patients with CKD [10,28,29].

We have previously reported an association between biomarkers reflecting LVH and LVDD and fluid overload in patients with CKD stage 5 [10,11]. Our previous studies did not examine each other's relationship on one axis by integrating all three factors (fluid balance, LV mass, and LV diastolic function). These studies analyzed the meaning of a single factor using only dependent, independent, and control variables. From the perspective of uremic cardiomyopathy, knowing the exact time when cardiac structural or functional changes can be a very important point in the treatment and prevention of complications. However, more importantly, because complications are not determined only by a single factor, a truly preventive approach is possible only when numerous factors are understood and judged in a complex manner. Statistically, multiple regression is an objective method that can empirically verify the influential factors. However, there is a limit to confirming the relationship between the statistically significant factors. Since the introduction of the moderation-mediation analysis, the relationship between the associated factors has been analyzed. Recently, analysis using the PROCESS macro and bootstrapping technique [18] instead of Baron and Kenny's method [12,30], which is often used in mediation analysis, has been accepted as a more advanced concept.

In a prospective longitudinal study over 1 year, advanced CKD stages 4 and 5 were more associated with larger cardiac changes, including increased LV mass and decreased diastolic function, compared with CKD stage 3 [7]. This study was performed to determine the importance of baseline CKD stages in predicting longitudinal changes in cardiac structure and function and not to evaluate which factors were involved. In our study, we first confirmed that CKD stage 5 had statistically significant differences in LVMI, OH/ECW, and E/e´ ratio compared with CKD stage 3 (Table 1). We confirmed that LVMI and OH/ECW had a statistically significant relationship with the E/e´ ratio (Table 2). The purpose of our study was to investigate the statistical significance of the latent mediating effect of the mediator on the association between the predictor and the dependent variable. Mediation analysis is possible only when the aforementioned three parameters have a significant correlation with each other. OH/ECW was positively correlated with LVMI ($p < 0.001$) in CKD stage 5, whereas there was no correlation with each other in CKD stage 3 ($p = 0.06$). This means that it was linked to the mediating analysis results that LVMI had no indirect effect on CKD stage 3. Considering the results reported by Cai et al. [7], it can be assumed that the pathophysiology of cardiac impairment becomes more complex as CKD progresses to an advanced stage. Our study demonstrated that mediation analysis could be a method for investigating complexity.

This study has some limitations. First, the number of

patients with CKD stage 3 was relatively small compared to that of patients with CKD stage 5. It could not be determined whether this had an effect on the analysis results for CKD stage 3. Additionally, the proportion of men was relatively higher than that of women. There was also a difference in the sex ratio between the two groups. Therefore, this may have affected the LV mass. Although sex was used as a correction factor in the analysis, sufficient consideration was not given to sex-specific differences in LV mass. Second, we did not measure these parameters in patients with CKD stage 4. Therefore, the significance of the mediation analysis on whether there was an indirect effect could not be confirmed for CKD stage 4. Third, we know that the association between fluid overload and diastolic dysfunction cannot be determined by a single echocardiographic study. While a concrete consensus on the treatment of diastolic dysfunction has not yet been established, blood pressure control, heart rate control, improvement of myocardial ischemia, and blood volume control are being emphasized [31]. Therefore, our study provides an opportunity to examine the relationship between fluid balance and a well-known risk factor for LVDD. Fourth, other variables that may mediate fluid balance may also exist, since our patients were accompanied by complicated combinations of risk factors, such as increased uremic toxin, systemic inflammation, and long-term hemodynamic instability. Furthermore, there may have been unmeasured confounding factors. These factors were not sufficiently considered in this analysis. Fifth, since the serial assessment of the predictor, mediator, and dependent variables was not performed over time, the role of the three factors according to the amount of change could not be identified. Finally, we are well aware that mediation analysis methods are limited in their ability to account for all of the complexity. It is clear that the results of statistical analysis can only support a hypothesis and do not prove it. Despite these limitations, the strength of our study is that it provided meaningful information that the indirect effect of the mediator may be different at different CKD stages. To our knowledge, this is the first study to attempt such an analysis.

Considering our results, we suggest that the evaluation of structural and functional cardiac abnormalities and volume status should be performed regularly and simultaneously across all stages of CKD. Further analyses of several other risk factors could provide insight into the mechanisms underlying the associations between associated factors, which could lead to the tailored application of treatment strategies and, hence, improve cardiovascular outcomes during the progression of CKD.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available upon reasonable request from the corresponding author.

Authors' contributions

Conceptualization: BGH
Data curation: BGH, JYL, JSK, JWY
Formal analysis: BGH, SWP
Project administration: BGH, JYL, JSK, JWY, SWP
Writing–original draft: BGH, SWP
Writing–review & editing: All authors
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References

1. Paoletti E, De Nicola L, Gabbai FB, et al. Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension. *Clin J Am Soc Nephrol* 2016;11:271–279.
2. Sharma R, Pellerin D, Gaze DC, et al. Mitral peak Doppler E-wave to peak mitral annulus velocity ratio is an accurate estimate of left ventricular filling pressure and predicts mortality in end-stage renal disease. *J Am Soc Echocardiogr* 2006;19:266–273.
3. Han JH, Han JS, Kim EJ, et al. Diastolic dysfunction is an independent predictor of cardiovascular events in incident dialysis patients with preserved systolic function. *PLoS One*

2015;10:e0118694.
4. Hickson LJ, Negrotto SM, Onuigbo M, et al. Echocardiography criteria for structural heart disease in patients with end-stage renal disease initiating hemodialysis. *J Am Coll Cardiol* 2016;67:1173–1182.
5. Kim MK, Kim B, Lee JY, et al. Tissue Doppler-derived E/e' ratio as a parameter for assessing diastolic heart failure and as a predictor of mortality in patients with chronic kidney disease. *Korean J Intern Med* 2013;28:35–44.
6. Nardi E, Palermo A, Mulè G, Cusimano P, Cottone S, Cerasola G. Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. *J Hypertens* 2009;27:633–641.
7. Cai QZ, Lu XZ, Lu Y, Wang AY. Longitudinal changes of cardiac structure and function in CKD (CASCADE study). *J Am Soc Nephrol* 2014;25:1599–1608.
8. Tsai YC, Chiu YW, Tsai JC, et al. Association of fluid overload with cardiovascular morbidity and all-cause mortality in stages 4 and 5 CKD. *Clin J Am Soc Nephrol* 2015;10:39–46.
9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–2200.
10. Kim JS, Yang JW, Yoo JS, Choi SO, Han BG. Association between E/e' ratio and fluid overload in patients with predialysis chronic kidney disease. *PLoS One* 2017;12:e0184764.
11. Han BG, Lee JY, Choi SO, Yang JW, Kim JS. Relative overhydration is independently associated with left ventricular hypertrophy in dialysis naïve patients with stage 5 chronic kidney disease. *Sci Rep* 2020;10:15924.
12. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173–1182.
13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
14. Nagueh SF, Smiseth OA, Appleton CP, 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.
15. Moissl UM, Wabel P, Chamney PW, et al. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006;27:921–933.
16. Chamney PW, Wabel P, Moissl UM, et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr* 2007;85:80–89.
17. Wabel P, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009;27:75–80.
18. Hayes AF, Scharkow M. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter? *Psychol Sci* 2013;24:1918–1927.
19. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociol Methodol* 1982;13:290–312.
20. Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychol Methods* 2002;7:422–445.
21. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 2009;24:1574–1579.
22. Edwards NC, Moody WE, Chue CD, Ferro CJ, Townend JN, Steeds RP. Defining the natural history of uremic cardiomyopathy in chronic kidney disease: the role of cardiovascular magnetic resonance. *JACC Cardiovasc Imaging* 2014;7:703–714.
23. Bansal N, Keane M, Delafontaine P, et al. A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study. *Clin J Am Soc Nephrol* 2013;8:355–362.
24. Park M, Hsu CY, Li Y, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol* 2012;23:1725–1734.
25. Huang JC, Tsai YC, Wu PY, et al. Independent association of overhydration with all-cause and cardiovascular mortality adjusted for global left ventricular longitudinal systolic strain and E/E' ratio in maintenance hemodialysis patients. *Kidney Blood Press Res* 2018;43:1322–1332.
26. Loutradis C, Sarafidis PA, Ferro CJ, Zoccali C. Volume overload in hemodialysis: diagnosis, cardiovascular consequences, and management. *Nephrol Dial Transplant* 2021;36:2182–2193.
27. Nitta K, Iimuro S, Imai E, et al. Risk factors for increased left ventricular hypertrophy in patients with chronic kidney disease: findings from the CKD-JAC study. *Clin Exp Nephrol* 2019;23:85–98.
28. Essig M, Escoubet B, de Zuttere D, et al. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrol Dial Transplant* 2008;23:239–248.
29. Sun L, Li Q, Sun Z, et al. Impact of overhydration on left ventric-

ular hypertrophy in patients with chronic kidney disease. *Front Nutr* 2022;9:761848.

30. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods* 2013;18:137–150.
31. Satpathy C, Mishra TK, Satpathy R, Satpathy HK, Barone E. Diagnosis and management of diastolic dysfunction and heart failure. *Am Fam Physician* 2006;73:841–846.