



# The correlation between serum fibroblast growth factor-23 levels and left ventricular hypertrophy in chronic kidney disease patients

Abdul Mubdi AA Karim<sup>1</sup>, Hasyim Kasim<sup>2</sup>, Akhyar Albaar<sup>2</sup>, Sitti Rabiul Zalia Ramadhan<sup>2</sup>, Nasrum Machmud<sup>2</sup>, Haerani Rasyid<sup>2</sup>, Pendrik Tandean<sup>3</sup>, Syakib Bakri<sup>2</sup>, Erwin Arief<sup>4</sup>, Tutik Harjianti<sup>5</sup>, Risna Halim<sup>6</sup>, Arifin Seweng<sup>7</sup>

<sup>1</sup>Department of Internal Medicine, Universitas Muslim Indonesia, Makassar, Indonesia

<sup>2</sup>Nephrology and Hypertension Division, Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia

<sup>3</sup>Cardiovascular Division, Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia

<sup>4</sup>Pulmonary and Intensive Care Division, Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia

<sup>5</sup>Hematology and Oncology Division, Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia

<sup>6</sup>Tropical Infection Division, Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia

<sup>7</sup>Department of Biostatistics, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia

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## ABSTRACT

**Introduction:** Hyperphosphatemia in chronic kidney disease (CKD) patients can stimulate the production of the fibroblast growth factor-23 (FGF-23) phosphatonin hormone, which is associated with cardiac remodeling resulting in left ventricular hypertrophy (LVH).

**Objectives:** To determine the correlation between FGF-23 level and LVH incidence in CKD patients and establish the associated risk factors.

**Materials and Methods:** This cross-sectional study involved 74 CKD patients who were classified as stage 3 (n=18), stage 4 (n=17), stage 3 (n=18), dialysis stage 5 (n=20), or non-dialysis stage 5 (n=19). The FGF-23 levels of the patients were measured using the ELISA (enzyme-linked immunosorbent assay) kit method, whereas a cardiologist verified LVH using an echocardiographic examination based on the LVH criteria of >95 g/m<sup>2</sup> for females and >115 g/m<sup>2</sup> for males.

**Results:** A significant difference was observed in the mean FGF-23 values between the LVH and non-LVH patients (443.27 ± 437.047 RU/mL and 172.68 ± 185.56 RU/mL, respectively;  $P < 0.05$ ). The receiver operating characteristics revealed that patients with FGF-23 levels >123.95 RU/mL had a 3.6 times greater risk of LVH compared to those with values ≤123.95 RU/mL. The LVH risk factors of gender and age, as well as hypertension, diabetes mellitus, and obesity diagnoses were not associated with LVH incidence in CKD patients.

**Conclusion:** A significant association was found between FGF-23 level and LVH incidence in CKD patients, in which an FGF-23 level >123.95 RU/mL corresponded to a 3.6 times greater risk of LVH than those with FGF-23 levels below this value.

### Implication for health policy/practice/research/medical education:

Hyperphosphatemia can occur in patients with chronic kidney disease and this leads to the stimulation of the FGF-23 phosphatonin hormone. This hormone is associated with cardiac remodeling that results in LVH. A significant association was found between FGF-23 level and LVH incidence in CKD patients, whereby FGF-23 levels >123.95 RU/mL were associated with a 3.6 times higher risk of LVH compared to patients with levels ≤123.95 RU/mL.

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## Introduction

The Kidney Disease Quality Outcome Initiative (K/DOQI) defines chronic kidney disease (CKD) as a structural or functional abnormality in the kidney that persists for over three months and affects the health of the patient (1). CKD can cause bone mineral disorders (i.e., secondary hyperparathyroidism). Decreased excretion by the kidney results in the secretion of a parathyroid and phosphatonin hormone (fibroblast growth factor-23, FGF-23) that reduces the increased phosphate levels (2). FGF-23 is associated with cardiovascular events in CKD patients (3,4).

Cardiac structural changes appear in CKD patients at stages 2 and 3, during which a thickening of the left ventricular wall occurs that affects diastolic function (5). FGF-23 activates the local renin-angiotensin-aldosterone (RAA) system in the heart that is involved in the remodeling of cardiac muscle (6-8). Through the induction of angiotensinogen and suppression of angiotensin-converting enzyme-2 (ACE-2) in the heart, FGF-23 activates the local RAA system in cardiac myocyte cells (8,9). Angiotensin II and aldosterone are considered stimulators of FGF-23 expression in cardiac muscle. Angiotensin II binds to the angiotensin II type 1 receptor (AT1R) in fibroblasts and cardiac myocytes, which induces growth factor (TGF- $\beta$ ) transformation in cardiac fibroblast cells, tissue matrix changes, and fibrosis and cell hypertrophy enhancements of cardiac myocytes (8). Numerous studies (10-16) investigated the relationship between FGF-23 and left ventricular mass enlargement of the heart.

## Objectives

The objectives of this study were to determine the correlation between FGF-23 level and LVH incidence in CKD patients and to identify the risk factors (hypertension, diabetes mellitus (DM), gender, and age) that were associated with FGF-23 level and LVH status in CKD patients.

## Patients and Methods

### Study design

This cross-sectional study was conducted at Hasanuddin university hospital, Wahidin Sudirohusodo hospital, and Ibnu Sina hospital, Makassar, Sulawesi Selatan, Indonesia. The participants were stage 3, 4, and 5 CKD patients who were or were not on dialysis, were outpatients or inpatients from April to November 2021, and met the research criteria. The inclusion criteria consisted of patients aged 18–65 years who consented to a blood test and echocardiography examination.

The serum of a patient (approximately 5 mL) was extracted using a disposable syringe and inserted into a serum tube that was labeled with the name, sample number, and date of collection. The tube was softly shaken 5–10 times until homogeneous and refrigerated for 30–45

minutes until frozen, during which time the blood from the next patient was processed.

The tubes were centrifuged 1000 rpm for 15 minutes and divided into 3 parts with a concentration of 1.5 mL for examination. Serum FGF-23 levels were determined using a human enzyme-linked immunosorbent assay (ELISA) kit (catalog no. 60-6100, Immotopics Inc., San Clemente, CA, USA) according to the manufacturer's instructions.

Blood samples were obtained at the Cardiac Centre, Wahidin Sudirohusodo hospital and echocardiography was performed by a cardiologist using a GE Vivid 95 Ultra Edition system (GE HealthCare, Chicago, IL, USA). The left ventricular hypertrophy (LVH) and diastolic function categories were based on the European society of cardiology criteria of  $>95$  g/m<sup>2</sup> for females and  $>115$  g/m<sup>2</sup> for males (17,18). The left ventricle mass index (LVMI) was determined using the formula of Cosyns et al (19).

### Statistical analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp, Armonk, NY, USA). The Mann-Whitney U test and chi-square test were conducted for the analysis. Determination of cut-off points and the FGF-23 sensitivity and specificity levels to LVH were determined using a receiver operating characteristics (ROC) curve. The results were considered significant at *P* values  $<0.05$ .

## Results

Seventy-four participants, consisting of thirty-eight male (51.4%) and 36 female (48.6%) CKD patients aged 18–65 years (average  $48.27 \pm 12.62$  years) were included in this study (Table 1). The participants were grouped according to the following stages; stage 3 (18 patients; 24.3%), stage

**Table 1.** Data distribution based on LVH risk factors

Variable	LVH, n (%)		P value*
	Yes	No	
Age (y)			
$\geq 60$	11 (78.6)	3 (21.4)	0.779
$< 60$	45 (75.0)	15 (25.0)	
Gender			
Male	32 (84.2)	6 (15.8)	0.079
Female	24 (66.7)	12 (33.3)	
BMI kg/m <sup>2</sup>			
Obesity	15 (18.3)	3 (16.7)	0.384
Non-obesity	41 (73.2)	15 (26.8)	
DM			
Yes	22 (78.6)	6 (21.4)	0.651
No	34 (73.9)	12 (26.1)	
Hypertension			
Yes	34 (81.0)	8 (19.0)	0.225
No	22 (68.8)	10 (31.3)	

LVH, Left ventricular hypertrophy; BMI, Body mass index; DM; Diabetes mellitus.

\*Chi-squared test.

4 (17 patients; 23.0%), stage 5 non-dialysis (19 patients; 25.7%), and stage 5 dialysis (20 patients; 27.0%). The range of FGF-23 levels was 19.70–2013.20 RU/mL (median 196.40 RU/mL). The LVMI ranged from 51.87–253.00 g/m<sup>2</sup> (median 117.71 g/m<sup>2</sup>) and relative wall thickness (RWT) ranged from 0.20–0.90 cm with a median value of 0.47 cm. This study found no significant association between LVH risk factors (age, gender, BMI, hypertension, and DM) and LVH in CKD patients ( $P > 0.05$ ; Table 1).

In this study, a significant difference in FGF-23 mean value was found between LVH ( $443.27 \pm 437.047$  RU/mL) and non-LVH patients ( $172.68 \pm 185.56$  RU/mL) ( $P < 0.05$ ; Table 2). The optimal cut-off point for FGF-23 level in LVH incidence was determined using an ROC curve, with the assumption that a higher level of FGF-23 leads to a greater incidence of LVH. The cut-off point for FGF-23 was 123.95 RU/mL with a sensitivity of 64% and specificity of 67% (Figure 1).

The cross-tabulation test (Table 3) revealed a relationship between the optimal FGF-23 cut-off point and LVH ( $P < 0.05$ ) with an odds ratio (OR) of 3.60 (95% CI 1.17–11.06); therefore, the participants who had FGF-23 levels  $>123.95$  RU/mL had a 3.60 times higher risk for LVH than those with FGF-23 levels  $\leq 123.95$  RU/mL.

## Discussion

In this study, the risk factors for LVH such as age, gender, BMI, hypertension, and DM were determined to be independent of LVH; therefore, these factors were deemed not to have affected the correlation between FGF-23 level and LVH incidence in CKD patients. Nitta et al (20) found that the incidence of LVH in non-diabetic CKD cases was not affected by age, gender, or hypertension status; however, body mass index was the most influential factor in that study.

The correlation between FGF-23 level and LVH incidence in this study was similar to that of Gutierrez et al (21), who found that increasing levels of FGF-23 were associated with LVH. Each 5% increase in heart muscle

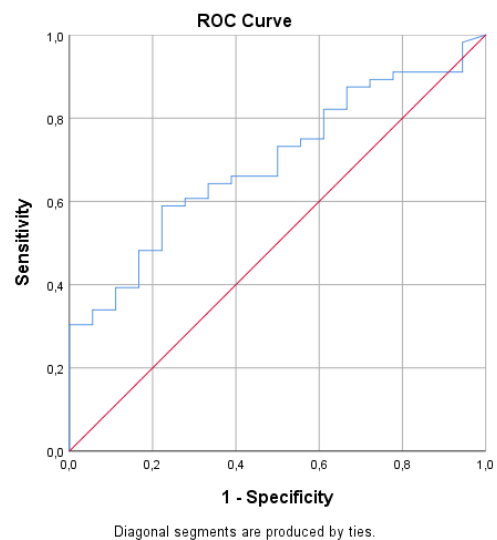


Figure 1. ROC graph of FGF-23 levels and LVH incidence.

mass was accompanied by an increment in FGF-23 level. A study also showed that middle and highest FGF-23 tertiles were associated with a 2.4 times greater incidence of coronary artery disease than those with low FGF-23 tertiles. Tanaka et al (22) found differences in mean LVMI values at each CKD stage based on FGF-23 tertile. Higher FGF-23 tertiles were associated with higher LVMI values in CKD patients.

A ROC curve was conducted to determine the optimal cut-off point of FGF-23 for the incidence of LVH, which was established as 123.95 RU/mL with a sensitivity of 64% and specificity of 67%. Mitsnefes et al (23) showed that FGF-23 levels higher than 147 RU/mL were associated with the occurrence of LVH. In addition, Seeherunvong et al (16) reported that FGF-23 levels above 100 RU/mL were related to an increased incidence of LVH, and Faul et al (14) derived a cut-off point of 142 RU/mL, which they found was associated with LVH in CKD patients. Sinha et al (24) determined an FGF-23 cut-off point of 168 RU/mL, and this was associated with LVH incidence in pediatric patients.

In this study, patients with FGF-23 levels greater than 123.95 RU/mL had a 3.6 times higher risk of LVH occurrence than those with FGF-23 levels below 123.95 RU/mL. Mirza et al (25) found that an FGF-23 level  $\geq 48.4$  pg/mL, which was classified as a tertile three group, had

Table 2. Mean levels of FGF-23 in the LVH group

Variable	LVH category		P value
	Yes	No	
FGF-23 (RU/mL)	443.27 $\pm$ 437.047	172.68 $\pm$ 185.56	0.014

RU, Relative units; FGF-23, Fibroblast growth factor-23, LVH, Left ventricular hypertrophy.

Table 3. Optimal FGF-23 cut-off point in relation to LVH status

Variable	LVH		P value*	OR**	95% CI
	Yes	No			
FGF-23 (RU/mL)					
$\geq 123.95$	36 (85.7)	6 (14.3)	0.021	3.60	1.17–11.06
$< 123.95$	20 (62.5)	12 (37.5)			

Note: LVH, Left ventricular hypertrophy; RU, Relative units; CI, Confidence interval; OR, Odds ratio; FGF-23, Fibroblast growth factor-23.

\* Chi-squared test, \*\* Cochran–Mantel–Haenszel test.

a 3.64 times greater risk of LVH than those with FGF-23 levels below 48.4 pg/mL. Furthermore, Gutiérrez et al (21) established that patients with FGF-23 levels above tertile three, >150 RU/mL, had 2.7 times greater risks for LVH than those with FGF-23 levels below this value.

Left ventricular hypertrophy in CKD patients contributes to the risk of morbidity or mortality from cardiovascular disease. Secondary hyperparathyroidism conditions increase fibrosis events in both the blood vessels and the heart, resulting in a decrease in cardiac contractility due to muscle stiffness of the heart, impaired systolic and diastolic function, and cardiac electrophysiological conduction disorders (26,27).

### Conclusion

An association was found between FGF-23 level and LVH incidence in CKD patients. Patients with FGF-23 levels greater than 123.95 RU/mL had a 3.6 times higher risk of LVH occurrence than those with FGF-23 levels below this value.

### Limitations of the study

A limitation of the study was that the samples were all obtained from CKD patients; therefore, we were not able to assess whether the heart defects occurred before or after the kidney disorders.

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### Authors' contribution

**Conceptualization:** Abdul Mubdi AA Karim, Hasyim Kasim, Akhyar Albaar, Sitti Rabiul Zatalia Ramadhan, Nasrum Machmud, Haerani Rasyid, and Syakib Bakri.

**Data curation:** Abdul Mubdi AA Karim.

**Formal analysis:** Abdul Mubdi AA Karim, Hasyim Kasim, and Arifin Seweng.

**Funding Acquisition:** Abdul Mubdi AA Karim.

**Investigation:** Abdul Mubdi AA Karim, Hasyim Kasim, and Arifin Seweng.

**Methodology:** Hasyim Kasim, Akhyar Albaar, Sitti Rabiul Zatalia Ramadhan, Nasrum Machmud, Haerani Rasyid, Syakib Bakri, and Arifin Seweng.

**Project administration:** Abdul Mubdi AA Karim.

**Resources:** AMK and Hasyim Kasim.

**Supervision:** Hasyim Kasim, Haerani Rasyid and Syakib Bakri.

**Validation:** Abdul Mubdi AA Karim and Arifin Seweng.

**Visualization:** Abdul Mubdi AA Karim.

**Writing—original draft:** Abdul Mubdi AA Karim, Hasyim Kasim, Akhyar Albaar, Sitti Rabiul Zatalia Ramadhan, Nasrum Machmud, Haerani Rasyid, Pendrik Tandean, Syakib Bakri, Erwin Arief, Tutik Harjianti, Risna Halim, and Arifin Seweng.

**Writing—review and editing:** Abdul Mubdi AA Karim,

Hasyim Kasim, Akhyar Albaar, Sitti Rabiul Zatalia Ramadhan, Nasrum Machmud, Haerani Rasyid, Pendrik Tandean, Syakib Bakri, Erwin Arief, Tutik Harjianti, Risna Halim, and Arifin Seweng.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

The research was conducted in compliance with the principles outlined in the Declaration of Helsinki and was approved by the Biomedical Research Commission on Human Ethics at the Faculty of Medicine, Hasanuddin University, with protocol number UH2077A624. Written informed consent was obtained from all participants prior to any intervention. Additionally, the authors have adhered to ethical standards, including avoiding plagiarism, data fabrication, and double publication.

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