

## Hepcidin-25 negatively predicts left ventricular mass index in chronic kidney disease patients

Yao-Peng Hsieh, Ching-Hui Huang, Chia-Ying Lee, Hung-Lin Chen, Ching-Yuang Lin, Chia-Chu Chang

Yao-Peng Hsieh, Chia-Chu Chang, Division of Nephrology, Department of Internal Medicine, Changhua Christian Hospital, Changhua City 500, Taiwan

Yao-Peng Hsieh, College of Management, MingDao University, Changhua 52345, Taiwan

Ching-Hui Huang, Division of Cardiology, Department of Internal Medicine, Changhua Christian Hospital, Changhua City 500, Taiwan

Chia-Ying Lee, College of Medicine, China Medical University, Taichung City 40402, Taiwan

Hung-Lin Chen, Department of Medical Nutrition Therapy and Food Service, Changhua Christian Hospital, Changhua City 500, Taiwan

Ching-Yuang Lin, Division of Pediatric Nephrology, China Medical University Hospital, Changhua 52345, Taiwan

Ching-Yuang Lin, Clinical Immunological Center, China Medical University Hospital, Changhua 52345, Taiwan

Chia-Chu Chang, School of Medicine, Chung Shan Medical University, Taichung City 40201, Taiwan

**Author contributions:** Hsieh YP provided the blood samples and wrote most of the manuscript; Lin CY and Chang CC designed the study and supervised all the processes; Huang CH performed the echocardiogram and interpreted the cardiovascular parameters; Chen HL and Lee CY performed the majority of experiments; Lin CY and Chang CC contributed equally to this work.

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**Correspondence to:** Chia-Chu Chang, MD, Division of Nephrology, Department of Internal Medicine, Changhua Christian Hospital, 135 Nanhsiao St., Changhua City 500, Taiwan. 27509@cch.org.tw

Telephone: +886-4-7238595 Fax: +886-4-7228289

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graphic and biochemical data, including the serum hepcidin-25 level, were collected for chronic kidney disease (CKD) patients. Two-dimensional echocardiography was performed to determine the left ventricle mass (LVM), left ventricular mass index (LVMI), interventricular septum thickness (IVSd), left ventricle posterior wall thickness (LVPW), right ventricular dimension (RVD), left atrium (LA) and ejection fraction (EF).

**RESULTS:** A total of 146 patients with stage 1 to 5 CKD were enrolled. Serum hepcidin-25 levels were  $16.51 \pm 5.2$ ,  $17.59 \pm 5.32$ ,  $17.38 \pm 6.47$ ,  $19.98 \pm 4.98$  and  $22.03 \pm 4.8$  ng/mL for stage 1 to 5 CKD patients, respectively. Hepcidin-25 level was independently predicted by the serum ferritin level ( $\beta = 0.6$ ,  $P = 0.002$ ) and the estimated glomerular filtration rate ( $\beta = -0.48$ ,  $P = 0.04$ ). There were negative correlations between the serum hepcidin level and the LVM and LVMI ( $P = 0.04$  and  $P = 0.005$ , respectively). Systolic blood pressure (BP) was positively correlated with the LVMI ( $P = 0.005$ ). In the multivariate analysis, a decreased serum hepcidin-25 level was independently associated with a higher LVMI ( $\beta = -0.28$ , 95%CI:  $-0.48 - -0.02$ ,  $P = 0.006$ ) after adjusting for body mass index, age and systolic BP.

**CONCLUSION:** A lower serum hepcidin level is associated with a higher LVMI in CKD patients. Low hepcidin levels may be independently correlated with unfavorable cardiovascular outcomes in this population.

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**Key words:** Hepcidin-25; Ferritin; Chronic kidney disease; Left ventricular mass; Left ventricular mass index

### Abstract

**AIM:** To assess the correlation between the serum hepcidin-25 level and left ventricular mass index.

**METHODS:** This study was a cross-sectional study conducted between March 2009 and April 2010. Demo-

**Core tip:** Cardiovascular disease is the primary cause of death among chronic kidney disease (CKD) patients, and left ventricular hypertrophy is a powerful independent predictor of mortality for end-stage renal disease patients. Low left ventricular performance is associated with iron deficiency anemia in rats with CKD.

Heparin-25, a recently discovered biologically active 25-amino acid peptide, plays a key role in the iron homeostasis. Chronic iron deficiency may, by itself, reduce exercise capacity and cause ultrastructural alterations in cardiomyocytes. In the study, we showed that patients in higher grade of CKD stage had the higher serum heparin levels, and that there was negative correlation between serum heparin level and LVMI.

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## INTRODUCTION

Heparin-25, a recently discovered biologically active 25-amino acid peptide, was first identified in human urine and plasma. This peptide contains four disulfide bonds<sup>[1]</sup>. It is synthesized, processed and secreted primarily by hepatocytes. *In vitro*, human heparin has anti-bacterial and antifungal activities<sup>[2]</sup>. Heparin regulates iron homeostasis by binding to and inducing the internalization and degradation of ferroportin, the sole cellular iron efflux channel in iron-transporting cells<sup>[3]</sup>. In experimental settings, pre-treatment with intravenous heparin or the induction of hepatic heparin expression prevents the inflammatory response due to exposure to lipopolysaccharide. Pagani *et al*<sup>[4]</sup> suggested that the inverse relationship between the levels of proinflammatory markers and circulating heparin may result from the anti-inflammatory properties of the latter<sup>[5]</sup>.

Iron is essential not only for erythropoiesis but also for several bioenergetic processes in skeletal muscle. Chronic iron deficiency may, by itself, reduce exercise capacity and cause ultrastructural alterations in cardiomyocytes<sup>[6]</sup>. Using multivariable Cox models, Jankowska *et al*<sup>[7]</sup> found that low heparin was independently associated with increased 3-year mortality among systolic heart failure (HF) patients. These authors also found a gradual reduction in the serum heparin level during the natural course of HF, accompanied by depleted iron stores (low serum ferritin) and iron-restricted erythropoiesis (reduced hemoglobin, high RDW). However, the possible mechanisms connecting the heparin level and cardiac mortality have not been addressed.

Cardiovascular disease is the primary cause of death among chronic kidney disease (CKD) patients<sup>[8]</sup>, and left ventricular hypertrophy is a powerful independent predictor of mortality for end-stage renal disease (ESRD) patients<sup>[9]</sup>. Low LV performance is associated with iron deficiency anemia in rats with CKD. Furthermore, the overproduction of HIF-1 $\alpha$  and the activation of caspase-3 seem to be associated with iron deficiency<sup>[10]</sup>. The correlation between the serum heparin level and cardiovascular risk was unclear for CKD patients.

The aims of this cross-sectional study were to use a

randomly selected subgroup of the CKD population: (1) to describe the variations in the serum heparin level by age, sex, body mass index (BMI), blood pressure (BP), and degree of renal insufficiency; and (2) to estimate the association between the serum heparin level and cardiovascular risk factors, including the BP, left ventricular mass (LVM) and left ventricular mass index (LVMI), in stage 1 to 5 CKD patients.

## MATERIALS AND METHODS

### Study population and design

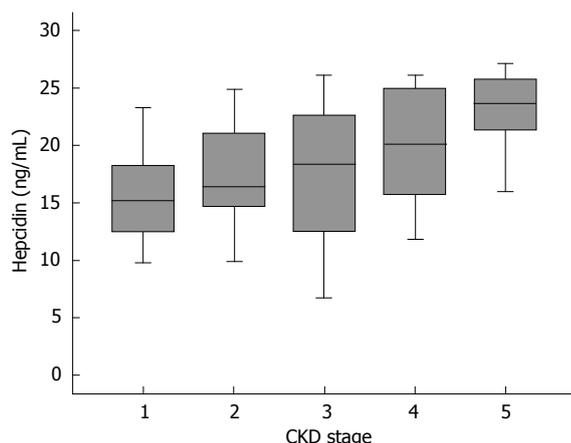
This study was a cross-sectional study conducted between March 2009 and April 2010 in the Nephrology Department of Changhua Christian Hospital and included 146 CKD patients (84 males, 62 females) in stages 1-5 who did not require dialysis. The estimated glomerular filtration rate (eGFR) was calculated by MDRD formula<sup>[11]</sup>. The stage was determined based on the eGFR and the level of proteinuria using the Kidney Disease Outcomes Quality Initiative (K/DOQI) definition. The patients had had stable renal function for at least 3 mo before recruitment. Exclusion criteria included hospitalization or infection during the past month, age below 18 years, chronic hepatitis, malignancy, active gastrointestinal bleeding or refusal to participate. All patients gave informed consent in advance, and the Institutional Review Board of the Changhua Christian Hospital (CCH) approved the protocol. This study was conducted in adherence with the Declaration of Helsinki.

Relevant clinical and biochemical data were retrieved from the patients' records and interviews. Demographic data included age, sex, BMI, the cause of the CKD, past medical history and medication history. The BP was measured daily with a random zero sphygmomanometer after a 15-min rest in the CKD unit. Participants with a systolic BP  $\geq$  140 mmHg, a diastolic BP  $\geq$  90 mmHg, or a history of hypertension and currently using antihypertensive drugs were categorized as hypertensive. Individuals with fasting plasma glucose levels  $>$  126 mg/dL or a history of diabetes mellitus and those currently using hypoglycemic drugs or insulin were categorized as having diabetes mellitus.

After fasting overnight for at least eight hours, a one-time blood sample was used to measure fasting blood sugar, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), blood urea nitrogen (BUN), creatinine, albumin, calcium, phosphate and hemoglobin. Samples were centrifuged immediately, and the supernatants were stored at -70 °C until further analysis. Two major types of heparin assays were available: mass spectrometry and ELISA. The plasma level of bioactive heparin-25 was measured in duplicate using a novel validated competitive ELISA (Peninsula Laboratories, LLC, United States).

### Echocardiography

Echocardiography was performed by a qualified cardiolo-



**Figure 1** Box plots of the serum hepcidin levels in different stages of chronic kidney disease. Patients with chronic kidney disease (CKD) stage 1 [ $n = 14$ , estimated glomerular filtration rate (eGFR) =  $123 \pm 22.5$  mL/min per  $1.73 \text{ m}^2$ ], CKD stage 2 ( $n = 16$ , eGFR =  $75 \pm 7.1$  mL/min per  $1.73 \text{ m}^2$ ), CKD stage 3 ( $n = 38$ , eGFR =  $43 \pm 10.1$  mL/min per  $1.73 \text{ m}^2$ ), CKD stage 4 ( $n = 34$ , eGFR =  $22 \pm 4.9$  mL/min per  $1.73 \text{ m}^2$ ), and CKD stage 5 ( $n = 44$ , eGFR =  $7.8 \pm 2.8$  mL/min per  $1.73 \text{ m}^2$ ). The boxes represent the first quartile, median, and third quartile of each group. Patients in each stage of CKD had significantly different hepcidin levels. In addition, subjects with higher CKD stages had higher serum hepcidin levels than those with lower CKD stages with a stepwise relationship.

gist using a Hewlett Packard Sonos 2000® (Hewlett-Packard Inc., Andover, MA) Phased-Array Imaging System with built-in software. The cardiologist was blind to the clinical data. The LVM, interventricular septum thickness (IVSd), left ventricle posterior wall thickness (LVPW), right ventricular dimension (RVD), left atrium (LA) and ejection fraction (EF) were determined according to the method established by the American Society of Echocardiography. We calculated the LVMI by dividing the LVM by height to the power of  $2.7(\text{g} \cdot \text{m}^{-2.7})$  because this formula has proven to be more accurate than the formula based on body surface area for predicting cardiovascular events. In this study, all echocardiographic measurements were performed by the same cardiologist at a single center to minimize the inter-observer variation.

### Statistical analysis

Values were expressed as the means  $\pm$  SD. Linear regression analysis was conducted to assess the relationships between the serum hepcidin level and other relevant parameters. Correlations were assessed using Spearman's or Pearson's test. To identify independent predictors of the serum hepcidin level, multiple regression analysis was performed. The parameters of different groups were compared using the Jonckheere-Terpstra or the Kruskal-Wallis test for non-parametric continuous data and an independent t-test for parametric data. Statistical analysis was performed using SPSS for Windows software, version 15.0. All tests were two-tailed, and a  $P$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

### Serum hepcidin levels and CKD stage

Table 1 presents the baseline demographic and clinical

**Table 1** Baseline clinical and laboratory data for 146 patients with chronic kidney disease<sup>1</sup>

Baseline clinical	Laboratory data
Age (yr)	61.7 $\pm$ 15.24
Female sex	62 (41.89%)
Systolic blood pressure (mmHg)	131.18 $\pm$ 13.2
Diastolic blood pressure (mmHg)	75.27 $\pm$ 10.51
Body mass index ( $\text{kg}/\text{m}^2$ ) <sup>2</sup>	24.99 $\pm$ 4.7
Hemoglobin (g/dL)	11.14 $\pm$ 2.16
BUN (mg/dL)	43.16 $\pm$ 23.56
Cr (mg/dL)	3.63 $\pm$ 3.19
eGFR-MDRD (mL/min per $1.73 \text{ m}^2$ of Body surface area) <sup>3</sup>	38.13 $\pm$ 35.24
CRP (mg/L)	0.223 $\pm$ 0.362
Ferritin ( $\mu\text{g}/\text{mL}$ )	254.59 $\pm$ 293.41
Iron ( $\mu\text{g}/\text{dL}$ )	74.6 $\pm$ 37.95
TSAT-percent <sup>4</sup>	0.28 $\pm$ 0.15
Albumin (g/dL)	3.96 $\pm$ 0.59
Fasting blood sugar (mg/dL)	116.9 $\pm$ 41.48
Uric acid (mg/dL)	7.71 $\pm$ 1.91
Calcium (mg/dL)	8.9 $\pm$ 0.56
Phosphate (mg/dL)	4.2 $\pm$ 1.57
Intact PTH (pg/mL)	291.97 $\pm$ 473.35
Total cholesterol (mg/dL)	176.31 $\pm$ 39.2
LDL cholesterol (mg/dL)	108.37 $\pm$ 35.8
HDL cholesterol (mg/dL)	49.35 $\pm$ 15.8
Triglycerides (mg/dL)	129.07 $\pm$ 73.96
IL-6 (ng/mL)	722.37 $\pm$ 205.53
Hepcidin (ng/mL)	19.42 $\pm$ 5.68

<sup>1</sup>Data given are the mean  $\pm$  SD; <sup>2</sup>The body mass index is the weight in kilograms divided by the square of the height in meters; <sup>3</sup>The estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula:  $186 \times [\text{serum creatinine (in micromoles per liter)}/88.4]^{-1.154} \times \text{age (in years)}^{-0.203} \times 1.21$  (if patient is black)  $\times 0.742$  (if patient is female); <sup>4</sup>The percent transferrin saturation was calculated as iron/total iron binding capacity (TIBC). BUN: Blood urea nitrogen; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; IL-6: Interleukin-6; PTH: Parathyroid hormone; CRP: C-reactive protein; TSAT: Transferrin saturation; Cr: Chromium; eGFR: Estimated glomerular filtration rate.

characteristics for all study participants ( $n = 146$ ). According to the National Kidney Foundation's classification of CKD, the patients were in the following stages: stage 1 for 14 patients, stage 2 for 16, stage 3 for 38, stage 4 for 34 and stage 5 for 44. The overall mean of eGFR was  $38.13$  mL/min per  $1.73 \text{ m}^2$ , and 30 patients were diabetic. Subjects with stage 4 or 5 disease had higher serum BUN, creatinine, phosphate, iPTH and hepcidin levels and lower a eGFR and hemoglobin level than subjects with earlier CKD stages ( $P < 0.05$  for all).

The serum hepcidin-25 levels were  $16.51 \pm 5.2$  ng/mL,  $17.59 \pm 5.32$  ng/mL,  $17.38 \pm 6.47$  ng/mL,  $19.98 \pm 4.98$  ng/mL and  $22.03 \pm 4.8$  ng/mL for subjects with stage 1, 2, 3, 4 and 5 CKD, respectively. There were marked differences in the serum hepcidin level between patients with different CKD stages, as determined by the Kruskal Wallis test ( $P = 0.039$ ). The serum hepcidin levels for patients in each CKD stage were significantly lower than those for patients in higher CKD stages, as determined by the Jonckheere-Terpstra test ( $P = 0.002$ ); *i.e.*, subjects in higher stages had significantly higher serum hepcidin-25 levels with a stepwise relationship (Figure 1). By contrast, there was no significant correlation,

**Table 2** Correlation of the serum hepcidin level with 2D echocardiography parameters in the multivariate analysis

Serum hepcidin level	<i>r</i>	<i>P</i> -value
LVMI	-0.514	0.005 <sup>1</sup>
LVM	-0.402	0.041 <sup>1</sup>
IVSd	-0.135	0.265
LVPW	-0.226	0.062
RVD	0.033	0.789
LA	0.015	0.904
EF	-0.018	0.882

All measurements were obtained using standard procedures: parasternal long axis view, parasternal short axis view, apical four-chamber view and apical five-chamber view. <sup>1</sup>*P* < 0.05 was considered statistically significant. LVM: Left ventricular mass; LVMI: Left ventricular mass index; IVSd: Interventricular septum thickness; LVPW: Left ventricular posterior wall thickness; RVD: Right ventricular dimension; EF: Ejection fraction; LA: Left atrium.

*via* the Kruskal Wallis and Jonckheere-Terpstra test, between each CKD stage and LVM and LVMI in our study. (Data not shown)

### Correlation between the serum hepcidin level and biochemical parameters

Pearson correlation analysis illustrated that the serum hepcidin level was strongly positively correlated with the serum BUN, creatinine, ferrous iron, phosphate, HDL and LDL cholesterol levels and negatively correlated with the eGFR and serum hemoglobin, albumin, and fasting blood sugar levels. There was no significant correlation between the serum hepcidin-25 level and the IL-6 or hsCRP level in our stable CKD patients (*r* = 0.183, *P* = 0.425; *r* = 0.19, *P* = 0.514, respectively). The multiple linear regression model plotted serum hepcidin *vs* BUN, creatinine, the iron profile, the eGFR, phosphate, HDL, LDL, hemoglobin, albumin and the fasting blood sugar level. Heparin was independently predicted by the serum ferritin level ( $\beta$  = 0.6, *P* = 0.002), the eGFR ( $\beta$  = -0.48, *P* = 0.04) and a CKD stage of 4-5 ( $\beta$  = 5.317, *P* = 0.035, *vs* CKD 1-3).

### Correlations between the serum hepcidin level and left ventricular mass and function

Table 2 shows the negative correlations between the serum hepcidin level and the LVM and LVMI (*P* = 0.04 and *P* = 0.005, respectively). No significant correlations with the IVSd, LVPW, RVD, LA and ejection fraction (EF) were found. The systolic BP was positively correlated with the LVMI (*P* = 0.005) and inversely correlated with the serum hepcidin level. No significant association between the hepcidin level and the diastolic BP was observed. After adjustment for BMI, age and systolic BP in the multivariate analysis, a decreased serum hepcidin level was only independently associated with a higher LVMI [ $\beta$  = -0.28, 95%CI: -0.48 - -0.02, *P* = 0.006].

## DISCUSSION

The major findings of our study are the following: (1)

there were negative correlations between the serum hepcidin level and both the LVM and LVMI; and (2) the hepcidin level was independently predicted by the serum ferritin level, the eGFR. By contrast, we did not find that there was significant correlation between each CKD stage and LVM and LVMI.

It is well-known that hepcidin expression is induced by inflammation or infection and is suppressed by anemia, hypoxia, iron and the use of erythropoiesis-stimulating agents<sup>[12,13]</sup>. However, there is an increasing number of emerging studies that show that iron deficiency itself inhibits the expression of hepcidin and its release into the circulation<sup>[14-16]</sup>. Weber *et al*<sup>[17]</sup> reported that hepcidin levels in the lower tertile were strongly associated with iron deficiency. As shown in the study, we also found that the hepcidin-25 level was positively correlated with the level of serum ferritin, a biomarker of iron loading and inflammation, in CKD patients. The subjects in our study population did not exhibit any signs of inflammation in the clinical and laboratory tests (hsCRP: 0.223 ± 0.362 mg/L). We hypothesized that a high circulating hepcidin-25 level can be interpreted predominantly as a response to excess iron, and this hypothesis is consistent with the results of a recent study<sup>[7]</sup>.

Iron is essential not only for erythropoiesis but also for several bioenergetic processes in skeletal muscle. Chronic iron deficiency may, by itself, reduce exercise capacity and cause ultrastructural alterations in cardiomyocytes<sup>[6]</sup>. Iron constitutes an important element of the enzymatic system of cardiomyocytes and can be stored inside these cells. Turner and colleagues have shown that rats with induced iron deficiency have increased cardiac output and sympathetic activation that subsequently result in left ventricular hypertrophy<sup>[18]</sup>. Dong *et al*<sup>[19]</sup> reported that left ventricular hypertrophy and dilatation occurring in iron-deficient (ID) rats is accompanied by mitochondrial swelling, irregular sarcomere organization, increased mitochondrial cytochrome c release and increased reactive nitrogen species production in cardiomyocytes. They found that after 20 wk of ID anemia, the rats developed maladapted cardiac hypertrophy with severe left ventricular dysfunction and exhibited signs of decomposition with lung congestion<sup>[19]</sup>. Dilated ventricles were characterized by myocardial interstitial fibrosis and increased myocardial expression of A-type natriuretic peptide (ANP) and BNP, as well as a reduced myocardial expression of collagen type 3 genes<sup>[20]</sup>. In the present study, we demonstrated that CKD patients with lower serum hepcidin-25 levels had greater LVMI and LVMs. The LVMI is the most reliable index of left ventricular hypertrophy (LVH), which can be diagnosed by either echocardiography or electrocardiography, and this condition is associated with cardiovascular morbidity and mortality<sup>[21,22]</sup>. Low LV performance is associated with iron deficiency anemia in rats with CKD<sup>[10]</sup>. To our knowledge, our study is the first work to analyze the serum hepcidin-25 level and echocardiography results in a group of adults with CKD.

Our study demonstrated that the serum hepcidin-25 level progressively increased with increase CKD severity, a finding consistent with the reports by Ashby *et al*<sup>[23]</sup> and

Zaritsky *et al.*<sup>[24]</sup> on the correlation between the hepcidin level and the eGFR. However, Peters *et al.*<sup>[25]</sup> measured the hepcidin level using radioimmunoassay and mass spectrometry-based methods, which were shown to be in close agreement ( $R = 0.96$ ,  $n = 99$ ) in a comparison study. In contrast, when using mass spectrometry to measure the hepcidin level, Peters *et al.*<sup>[26]</sup> concluded that the serum hepcidin-25 levels in CKD patients were independent of the GFR, and they attributed the discrepancy to the inability of the immunoassay used by Ashby to differentiate between isoforms and to differences in the study populations. We believe that further efforts to standardize the hepcidin assays are needed to resolve these differences.

The cytokine IL-6 is a key inducer of hepcidin synthesis during inflammation, both in mouse and human models<sup>[3,27]</sup>. No correlation was found between the hepcidin and TNF- $\alpha$  levels. Hepcidin levels in the lower tertile were found to be strongly associated with iron deficiency (OR = 16.5, 95%CI: 2.2-121.2;  $P < 0.01$ )<sup>[17]</sup>. Our findings are in accordance with these data: we found no significant correlation between the serum hepcidin-25 level and the IL-6 or hsCRP level in our stable CKD patients.

There are several limitations that needed to be recognized in the present study. Firstly, exogenous administration of erythropoiesis-stimulating agents (commonly for those with advanced CKD) promotes RBC synthesis, thus inhibiting hepcidin gene expression. In the present study, the impact of exogenous erythropoietin was not taken into account. Secondly, this study was limited by its cross-sectional nature, thus preventing the evaluation of causation in the association between the serum hepcidin level and cardiovascular risk. This shortcoming will be overcome as the larger participants in the future CKD study continue longitudinal follow-up with repeated measurements of the serum hepcidin-25 level.

In conclusion, this preliminary cross-sectional analysis demonstrated that the increase in the serum hepcidin level with CKD progression in adults is associated with a decreasing LVMI. Lower hepcidin-25 level may be independently associated with unfavorable cardiovascular outcomes for this population.

## COMMENTS

### Background

Cardiovascular disease is the primary cause of death among chronic kidney disease (CKD) patients, and left ventricular hypertrophy is a powerful independent predictor of mortality for end-stage renal disease patients. Low left ventricular performance is associated with iron deficiency anemia in rats with CKD. Hepcidin-25, a recently discovered biologically active 25-amino acid peptide, plays a key role in the iron homeostasis. Chronic iron deficiency may, by itself, reduce exercise capacity and cause ultrastructural alterations in cardiomyocytes. However, the correlation between the serum hepcidin level and cardiovascular risk was unclear for CKD patients.

### Research frontiers

Iron deficiency is frequent among patients with stable systolic heart failure, and associated with serious unfavourable clinical consequences. Jankowska *et al* found an early stage of heart failure was characterized by increased circulating hepcidin level and the progression of heart failure is connected with the decline in circulating hepcidin and the development of iron deficiency. In addition, low hepcidin was independently associated with increased 3-year mortality among

heart failure patients. The studies addressing the issue of iron status and cardiac performance were sparse in CKD patients.

### Innovations and breakthroughs

The serum hepcidin level increases gradually with the increment of CKD severity, suggesting the decreased excretion of hepcidin due to the decline in renal function. This is in accordance with previous researches. Left ventricular mass index, a powerful predictor of cardiovascular mortality, was shown to be negatively correlated with serum hepcidin level among our CKD patients comprising all 5 stages of CKD. Hepcidin is a key regulator of iron metabolism but accumulates with the decline in renal function. The complex mechanisms linking hepcidin and left ventricular mass index (LVMI) in CKD warrants further investigation.

### Applications

The study results that there was a negative correlation between LVMI and serum hepcidin level in CKD patients suggests hepcidin is a potential therapeutic target for the treatment and prevention of left ventricular hypertrophy in the future.

### Terminology

LVMI: left ventricular hypertrophy (LVH) is a common finding in patients with chronic kidney disease. echocardiographic criteria for the diagnosis of left ventricular hypertrophy were largely based on M-mode echocardiography and included a left ventricular mass index  $\geq 134$  and  $\geq 110$  g/m<sup>2</sup> body surface area in men and women, respectively. The presence of LVH (on electrocardiogram or echocardiography) is usually associated with increases in the incidence of heart failure, ventricular arrhythmias, decreased LV ejection fraction, sudden cardiac death, and aortic root dilation.

### Peer review

This interesting study demonstrates that serum hepcidin level is associated with left ventricular mass index, a powerful predictor of cardiovascular mortality in the general population. The linkage between hepcidin and left ventricular performance provides a potential therapeutic target to improve survival in CKD patients.

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